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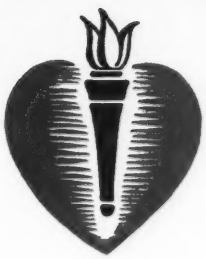

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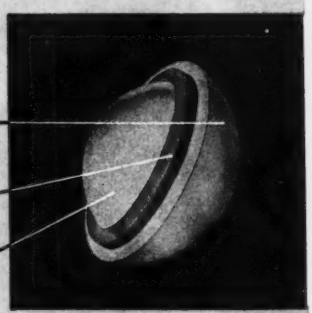

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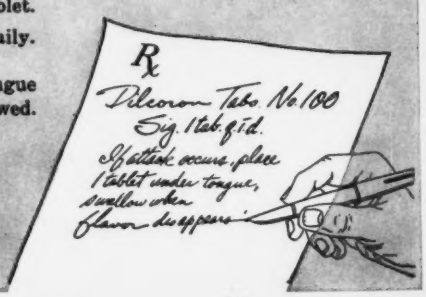

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Editorial

New Aspects and Problems in Interpreting Arrhythmias

THERE are 3 pillars upon which our present understanding of irregularities of the heart beat rests: 1. The recognition of a system of special myocardial fibers, part of which serves as a lone bridge to link the myocardium of the atria with that of the ventricles. 2. The property of all portions of this special system to create impulses and transmit them forward and backward. 3. The presence at the start of each cardiac cycle of a period of gradually lessening unresponsiveness to stimulation, a phase of absolute and relative refractoriness, that may become unduly prolonged under abnormal circumstances. The integration of these structural and functional characteristics for the background of a rational interpretation of cardiac arrhythmias is the result of the joint efforts of anatomists, physiologists, and clinicians in the past. This has been greatly aided by the introduction of an adequate tool, the electrocardiograph, to register experimental and bedside observations.

This "classical" period of arrhythmia research left a number of fundamental problems unsolved or only poorly understood. Biological processes underlying impulse formation in primary and subsidiary pacemaker regions remained completely unknown. The mechanism of delayed transmission of impulses through the A-V junctional tissues under normal and pathologic conditions was not known and was subject to various hypotheses. Little understanding existed about the variability of the refractory phase in different parts of the heart. Theories were proposed to explain the commonest types of irregular heart beat, such as flutter, fibrillation, and coupled premature systoles, but there was no general agreement as to their validity. Short of new methods of investigation, arrhythmia research seemed to have arrived at a dead end, and this was restricted to the collection of interesting specimens and unusual examples—only some of which could be interpreted on the basis of existing knowledge, the remainder could not. During this time, new problems in clinical electrocardiography were realized to lack thorough experimental exploration, e.g., the riddle of ventricular preexcitation and of disorders of rhythm associated with it; the mechanisms underlying partial (concealed) conduction into the A-V junction and of aberrant conduction within the ventricles; the existence of a supernormal phase and a "vulnerable" period in the cycle of the human heart; the dependence of certain irregularities of rhythm on derangements in the electrolyte equilibrium.

Progress in technology in recent years and the introduction of refined methods of anatomic and physiologic investigation have provided avenues for a fresh approach to these problems, as well as for testing the validity of classical concepts. The anatomist contributed new dissection technics permitting syste-

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matic examination of the structure of the specific system on a large scale in normal and abnormal autopsy material.[1, 2] The physiologist, taking advantage of high fidelity electronic recording systems, has supplied methods: (1) to explore the function of impulse creation and propagation in areas deeply buried within the beating heart, and (2) to study the bioelectric behavior of living cardiac tissues at the cellular level.[3] Even "in vitro" models have been devised, e.g., the imitation of abnormal patterns of A-V nodal function by varying interplay of oscillators in an electronic analog.[4]

The impact of this new era of experimental research is being felt in all aspects of clinical electrocardiography and cannot go unnoticed, especially by the investigator concerned with mechanisms of disorders of rhythm in man. Consequently, an attempt is made in this review (a) to compare, from the clinical standpoint, newly gained knowledge with concepts currently applied in the interpretation of arrhythmias, (b) to outline some areas in which presently held views have been fortified, and (c) to present other ideas that require revision or appear entirely untenable, in the light of recently established facts.

Morphology and Function of Conduction System

The existence of a specific muscle system in the heart, doubted by some, has now been fully confirmed and its principal structure has been found to correspond to the original descriptions. However, in the course of renewed systematic studies, muscular connections, previously unknown, were detected linking the A-V node and the common A-V bundle to the left ventricle.[5] Conceivably, such "paraspecific" fibers could serve as potential short-cuts for atrioventricular impulse transmission which bypass ordinary channels of ventricular activation. Recognizing the availability of more than a single anatomic path between atria and ventricles, which could have different conductivity properties, is important from two standpoints. On the one hand, it provides support for the existence of dual types of A-V conduction, first implied by clinical observers,[6–8] and lately also by physiologists[9–11] in explaining (a) reciprocal beating ("echo phenomena"), (b) some paradoxical features of forward and retrograde A-V conduction with rapid heart rates, and (c) the occurrence of aberrant ventricular conduction with slow heart rates. On the other hand, it may be necessary to revise some current principles applied in the distinction between various supraventricular and ventricular ectopic rhythms and mechanisms determining aberrant ventricular conduction in general.[12] However, neither the implication of functioning paraspecific fibers nor the assumption of 2 pathways within the A-V node, having different conduction rates, can account for all the problems posed by the preexcitation syndrome—especially by its associated disorders of rhythm. Here an abnormal, congenitally displaced, accessory A-V connection remote from the ordinary conduction system appears to be in operation.[8, 13–15]

Important advances have been made in the understanding of the functions of the specific system as a generator and propagator of the cardiac impulse. In single specific fibers, slow diastolic loss of membrane charge, a "prepotential," is demonstrable by microelectrodes, which precedes and initiates the characteristic rapid upstroke of the action potential.[16] In aggregates of specific fibers, such as the S-A and A-V node, the sum total of such spontaneously developing action potentials seems to be reflected in the form of rapid oscillatory electric activity, preceding depolarization of the surrounding myocardium.[17] However, this spontaneous activity seems to differ from that triggered by extraneous stimulation. When impulses initiated in the atria were traced in their passage through the A-V node, slow rising potential changes were recorded with extracellular[18] as well as intracellular[19] electrodes. Furthermore, in single specific fibers, the switch from propagated to spontaneous (pace

maker) activity was observed to be associated with a change in the shape and size of the action potential and the development of a diastolic potential. On this basis, the idea can be entertained that bioelectric phenomena resulting from intrinsic activity of nodal fibers are different from those from extrinsic activity. And since the maximal delay of normal and abnormal impulses can now be localized with reasonable certainty to fibers joining atrial and nodal myocardium, some insight has been gained into the ways by which the A-V node accomplishes its double function. Experimental investigation now seems feasible on conjoint or dissociated disorders of impulse formation and conduction which the clinician knows well do occur following inflammation, ischemia, and drug action.[20]

Refractory and Supernormal Phase

Much of the efforts of the physiologist in recent years has been devoted to detailed analysis of the mode and speed of recovery of atrial, ventricular, and A-V junctional tissues from complete unresponsiveness following depolarization to the point of restitution of normal excitability. New data have been accumulated with exact methods of recording, some in experiments performed on single myocardial fibers,[21] which must have a direct bearing on the understanding of disorders of rhythm in man. For, although little is known about the behavior of the refractory period in the human heart, its operation has to be implied in the analysis of the consequences of abnormal "active" and "passive" ectopic rhythms, in primary conduction disorders, and in the explanation of flutter and fibrillation. The validity of such empirical deductions in clinical electrocardiography can now be checked against precise newly established experimental facts, as illustrated in the following examples.

When the well-known effects of stimulation rate upon the duration of the refractory period of atria, ventricles, and the A-V node were submitted to new investigations, shortening or lengthening of the refractory phase dependent upon cycle length was found to take place abruptly, and not in a cumulative manner.[22] Furthermore, it was demonstrated in the dog's ventricle that alterations of the absolute and relative refractory phases are not necessarily parallel but may take place separately and to different extents.[23] Applied to clinical electrocardiography, these experimental data lend support to the interpretation of some commonly encountered phenomena: (a) the preferential occurrence, particularly in atrial fibrillation, of aberrant ventricular conduction when a short cycle follows a particularly long one—which has sometimes been mistaken for coupled beats of ectopic origin,[12] and (b) the maximal increment of conduction time in the second beat after an intermission in Wenckebach periods—resulting in a particular ventricular arrhythmia in A-V block, and atrial arrhythmia in S-A block.[6] On the other hand, the experimental finding of unrelated variability of the absolute and relative refractory phases provides a basis for the thesis that abnormal prolongation of either the relative or the absolute refractory phase, or of both, in the junctional tissues may be responsible (a) for different degrees of A-V block, and (b) for the occurrence of 2 types of second degree A-V block, one with and the other without progressive P-R prolongation.[6]

The operation of a phase of supernormality has been invoked in clinical electrocardiography (1) in the explanation of coupled premature beats ("extrasystoles") and of paroxysms of ectopic tachycardia as a result of repetitive response to a single stimulus, and (2) in the interpretation of "paradoxical" enhancements of depressed atrioventricular or intraventricular conductivity early in the cardiac cycle. The use of the same term for 2 totally different events—one referring to impulse formation, the other to impulse transmission—may have some justification because of the factor common to both, namely, a short-lasting enhancement

of function. However, an inadequacy of such a terminology becomes evident when the timing of the 2 supposed mechanisms relative to the recovery state of cardiac tissues is considered. Supernormal conductivity has been found to occur only in *depressed* heart tissues *within* the calculated range of an *abnormally prolonged* refractory phase, while, contrariwise, a phase of supernormal excitability causing coupled premature beats has been postulated to occur in *normal* hearts coincident with the U wave, *after* the normal refractoriness following the primary response has ended.

This dilemma in concept and semantics can perhaps be resolved by taking into account the details of the recovery process as explored experimentally with improved and sensitive registration methods. Short periods of hyperexcitability ("dips") were found in the recovery curves of atrial and ventricular myocardium during the time of the absolute refractory phase, toward the end of the relative refractory phase, and sometimes after the completion of the latter.[3] No such data are known for A-V nodal tissue, but a supernormal phase has been seen at the end of the action potential in isolated Purkinje fibers.[16] On this basis, the notion could be entertained of a modulation of the over-all process of recovery by superimposed oscillatory (metabolic) events on the cell membrane[3] resulting in momentary fluctuations of excitability or conductivity. A common background thus can be visualized, and a common valuable term maintained, for two processes seemingly distinct in their timing within the cardiac cycle.

Animal Experiments vs. Human Pathology

The applicability of data gained under artificially created experimental conditions to phenomena of human physiology and pathology may be questioned. As far as the refractory period of the heart is concerned, this jump seems to be feasible, since no fundamental difference in the behavior of refractoriness under various circumstances has been found in cardiac tissues of the various animal species. Moreover, in an ingeniously devised experiment, no difference could be detected in the responses of cardiac fibers to direct electrical stimuli and to impulses propagated from neighboring tissues.[2] However, such clinical extrapolation of experimental data may be misleading in other areas of investigation, particularly those dealing with specific disorders of cardiac rhythm, as exemplified by recent developments in the controversial field of the mechanisms of atrial flutter and fibrillation. On the basis of the ability to reproduce all known types of atrial arrhythmias in the normal dog heart by topical application of aconitine and other chemicals, the circus-movement theory of flutter and fibrillation had been completely abandoned by some investigators in favor of the theory of a single, rapidly discharging ectopic focus.[24] However, a circulating wave has clearly been demonstrated by others, in the interim, in atria in which flutter was induced electrically after severe mechanical damage.[25, 26] Furthermore, the operation of a rapidly firing focus and a circus movement could be observed, side by side, in some preparations.[27] Thus, these two mechanisms, clearly distinguishable on the basis of different reactions to mechanical, thermic, and cholinergic influences, are not mutually exclusive. In fact one, the circus movement, could be initiated and sustained by the other, as a secondary mechanism characteristic for syncytial tissues. This occurs when the heart is exposed to very rapid stimulation, resulting in relaxation, unlike skeletal muscle which reacts with a tetanic contraction. In any case, it would appear at present that aconitine-produced flutter and fibrillation and that induced by electrical stimulation are two different processes, either of which may occur in the human heart. The possibilities of distinguishing the two in clinical electrocardiograms on the basis of the configuration of the atrial deflections have been pointed out.[28]

This brief review has touched upon some accomplishments of recent anatomic and experimental research which should be welcome to the clinician because it shows him ways to handle unsolved problems, old and new. Unfortunately, other clinical problems have not yet been considered by the experimentor employing these modern methods, perhaps because he may not be aware of the potentialities of his new tools in attacking and unfolding the mechanisms operating in the diseased human heart. Some of these problems are posed by the following questions: What is the mechanism of coupled premature beats? Is it a re-entry process or a multiple response? After all, cannot one or the other take place distal to a depressed myocardial region, the common postulate[6, 24] of the 2 prevalent but divergent theories? What is the nature of the protective mechanism that permits continuous undisturbed parasystolic activity of an ectopic center? If normal and abnormal retardation of impulse transmission from the atria to the ventricles is to be localized in the atrio-nodal junction, then what is the nature of concealed A-V conduction? Is it a gradual decrement of impulse intensity, or an increment of excitation threshold in successive elements of conducting tissues, that permits the impulse to traverse the greatest obstacle, penetrate deeply into its path, but prevents it from reaching its destination? Is the short-lasting action potential of single nodal fibers a correct measure of the refractory period of the entire A-V junction, or rather would it be that nodal tissue has the property of producing weak, nonpropagated potentials—early in the cycle under normal conditions, and for a protracted period in depressed and diseased states? And, finally, is it possible to quantitate at cellular levels the potassium-digitalis relationships that enhance or suppress impulse formation in ectopic centers? These are but some of the most burning fundamental questions one is faced with in everyday clinical electrocardiography. They pose a challenge inviting closer cooperation and exchange of ideas among physiologists and clinical investigators—an exchange somewhat lacking in the past.

ALFRED PICK
RICHARD LANGENDORF
LOUIS N. KATZ

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THE TORCH BEARERS

Alfred Noyes
English poet, 1880-

Herschel
Who that once has seen
How truth leads on to truth, shall ever dare
To set a bound to knowledge?—*Watchers of the Sky.* From *Great Companions. Readings on the Meaning and Conduct of Life from Ancient and Modern Sources.* Vol. I, Boston, The Beacon Press, 1952.

Supravalvular Aortic Stenosis

Clinical, Hemodynamic and Pathologic Observations

By ANDREW G. MORROW, M.D., JOHN A. WALDHAUSEN, M.D., ROBERT L. PETERS, M.D., ROBERT D. BLOODWELL, M.D., AND EUGENE BRAUNWALD, M.D.

In 3 patients obstruction to left ventricular outflow was shown to be due to a localized narrowing of the aortic root at the point of insertion of the aortic leaflets. The site of obstruction was localized by left heart catheterization and selective angiography. The pathologic findings in 2 patients are described and the problem of the surgical management of this unusual form of aortic stenosis is discussed.

PREVIOUS reports[1, 2] have dealt in detail with the clinical and hemodynamic findings in patients with obstruction to left ventricular outflow caused by congenital valvular or subvalvular aortic stenosis. More recently it has been shown that a systolic pressure gradient between the left ventricle and aorta may also result from functional obstruction in the outflow tract of the ventricle secondary to massive left ventricular hypertrophy.[3-5] Among the group of patients with congenital aortic stenosis who have been studied at the National Heart Institute, 3 have been shown to have obstruction to outflow caused by a constriction in the aorta itself immediately distal to the valve. In the present report the results of diagnostic studies in these 3 patients are described and the pathologic findings in 2 of them are presented.

CLINICAL SUMMARIES

1. J. R., an 8-year-old girl was, first admitted to the National Heart Institute in November 1956, known to have a heart murmur since birth. Her growth and development have been markedly retarded (her weight was below the third percentile on a standard grid) and she had been subject to frequent respiratory infections. The heart was enlarged and the point of maximal impulse was in the sixth intercostal space in the midclavicular line. A systolic thrill was palpable at the base of the heart and over the carotid arteries. The second heart sound in the pulmonary area was accentuated and split. A grade-IV/VI systolic ejection murmur was heard best along the right sternal border and was transmitted to the neck. The rhythm was regular. The blood pressure in the right arm was 106/16 and in the left arm 112/0 mm. Hg. The electrocardiogram revealed sinus tachycardia, left ventricular hypertrophy, right axis deviation, and P waves suggestive of right atrial enlargement. Fluoroscopic and radiographic examinations demonstrated enlargement of both ventricles. The aorta was not dilated. At right heart catheterization the pulmonary artery pressure was 70/24 mm. Hg, and the catheter was passed through a patent ductus into the descending aorta. A retrograde thoracic aortogram was carried out (fig. 1). The sinuses of Valsalva appeared normal, and there was an apparent constriction of the aortic root immediately above them. Some left ventricular opacification indicated mild coexisting aortic regurgitation. The aorta itself was smaller than normal. The patent ductus was again demonstrated.

In February 1957 the patent ductus was closed through a posterolateral thoracotomy. Although the aortic root could not be inspected, a pressure gradient between the left ventricle and aorta following closure of the ductus was confirmed by simultaneous pressure measurements. The left ventricular pressure at this time was 194/10 mm. Hg and the peak systolic gradient was 81 mm. Hg.

In the 2 years following this operation, the child experienced no further serious respiratory infections but still failed to grow and gain weight. She began to complain of fatigability and became dizzy with strenuous exercise on several occasions. She was readmitted to the Institute in July 1958 for re-evaluation and aortic valvulotomy.

The physical findings on this occasion revealed a blood pressure of 96/80. The classic thrill and murmur of aortic stenosis were present, and the

From the Clinic of Surgery, National Heart Institute, and the Department of Pathological Anatomy, the National Institutes of Health, Bethesda, Md.

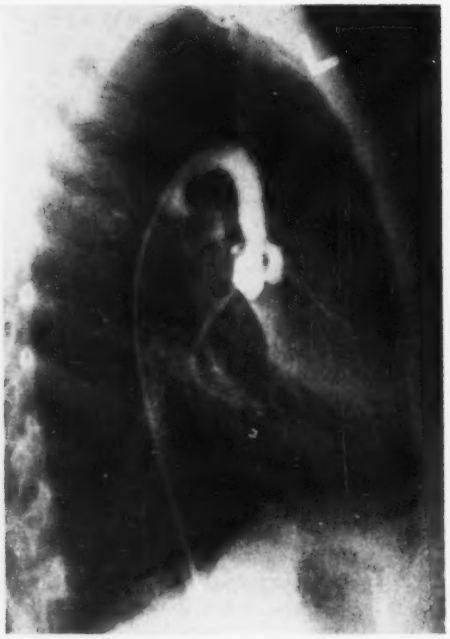


FIG. 1. Lateral view of the thoracic aortogram (*top*) and its schematic interpretation (*bottom*) obtained in patient J.R. The supravalvular area of constriction is indicated.

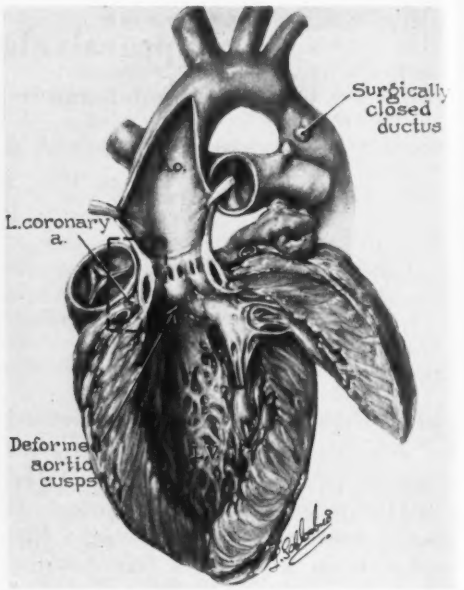


FIG. 2. Drawing of the heart and aorta of patient J.R. The constriction at the upper margins of the sinuses of Valsalva and the valve deformity are shown. The enclosed area is shown microscopically in figure 3.

second heart sound in the aortic area was diminished in intensity. Another right heart catheterization was performed; the pulmonary artery pressure had fallen to 45/8 mm. Hg, and absence of a left-to-right shunt was shown by a pulmonary artery nitrous oxide test of 1 per cent.[6] Percutaneous puncture of the left ventricle[7] was carried out under general anesthesia. The peak systolic gradient between the left ventricle and femoral artery was 52 mm. Hg. Operation for relief of the supravalvular obstruction was recommended but on the morning of the scheduled procedure the child had cardiac arrest on the ward and attempts at resuscitation were unsuccessful.

Pathologic Description. The heart weighed 200 Gm. and both ventricles were hypertrophied. The aorta and pulmonary artery were in normal position and there were no abnormalities of the chambers or septa. The deformities of the aortic valve and ascending aorta which produced stenosis are illustrated in figure 2. There were 3 normal-sized but thickened valve leaflets. A fibrous band originated at the center of the free edge of each leaflet and inserted into the thickened aortic intima plica at the upper margin of the sinuses of Valsalva. The resulting shelf-like thickening narrowed the aortic orifice to a diameter of 5 mm

Above the stenosis the aorta was 10 mm. in diameter.

The microscopic appearance of a vertical section through the left coronary leaflet is shown in figure 3. There was considerable fibrous thickening of the upper portion of the leaflet. The nodule of Arantii was absent and the sinus of Valsalva was bridged by a band of dense connective tissue that inserted into the intima of the thickened aorta at the upper margin of the sinus. An area of subendothelial fibrosis in the base of the sinus resembled a "jet" lesion. There was moderate coronary arteriosclerosis.

2. E. B., was an 18-year-old boy in whom a murmur had first been noted immediately after birth. At the age of 7 years he developed subacute bacterial endocarditis and pneumococcus type IV was cultured from his blood. The infection was cured by the administration of penicillin and he had no symptoms until age 17, when he experienced sudden severe precordial pain and was hospitalized for 3 days. A chest x-ray is said to have shown a calcified aneurysm of the ascending aorta. The patient had no further chest pain or limitation of activity and was asymptomatic at the time of his first admission to the National Heart Institute a year later.

Physical examination at this time revealed normal development and was unremarkable except for the cardiovascular system. The heart was enlarged and the point of maximal impulse was in the sixth left intercostal space outside the midclavicular line. A left ventricular lift was palpable at the apex and a systolic thrill was felt to the right of the sternum and over the carotid vessels. The aortic second sound was decreased and a grade-V/VI harsh systolic ejection murmur was audible over the entire precordium; it was of maximal intensity in the second and third right intercostal spaces. Blood pressure in the right arm was 110/70 mm. Hg and in the left arm 90/60. The peripheral pulses were palpable and the rhythm was regular.

The electrocardiogram revealed left bundle-branch block and there were occasional premature ventricular contractions. Fluoroscopic and radiographic examinations of the chest demonstrated appreciable enlargement of the left ventricle, and a calcified mass was seen to the right of the aortic arch. Right heart catheterization revealed a pulmonary artery pressure of 20/8 mm. Hg and the pulmonary artery nitrous oxide test was negative (15 per cent). The cardiac output at rest was 2.26 L. per minute per M.^{2} and on exercise rose to 4.26 L. per minute per M.^{2} Left heart catheterization was carried out by the transbronchial method.[8] The mean left atrial pressure was 12 mm. Hg and its contour was normal. The left ventricular pressure was 300/15 mm. Hg and the right radial artery pressure, measured simultaneously, was 155/86 mm. Hg, resulting in a peak systolic gradient of 145 mm. Hg. The cardiac

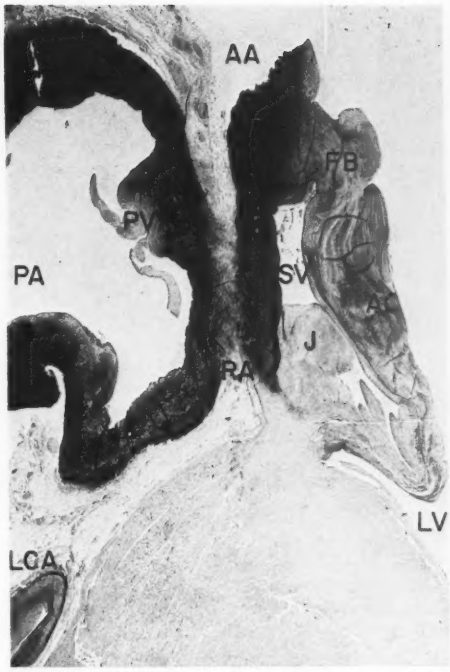


FIG. 3. Photomicrograph of section through the left coronary leaflet of the aortic valve in patient J.R. Orientation as illustrated in figure 2. *PA*, pulmonary artery; *PV*, pulmonary valve; *LV*, left ventricular cavity; *AA*, ascending aorta; *RA*, root of aorta; *AC*, left coronary aortic leaflet; *SV*, sinus of Valsalva; *FB*, fibrous band attaching leaflet to aortic wall.; *J*, jet lesion in base of sinus; *LCA*, left anterior descending coronary artery. Orecin-hematoxylin, × 6.5.

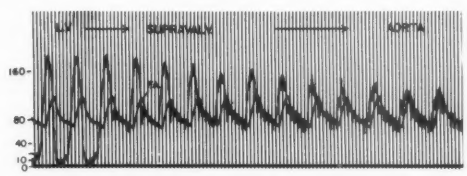
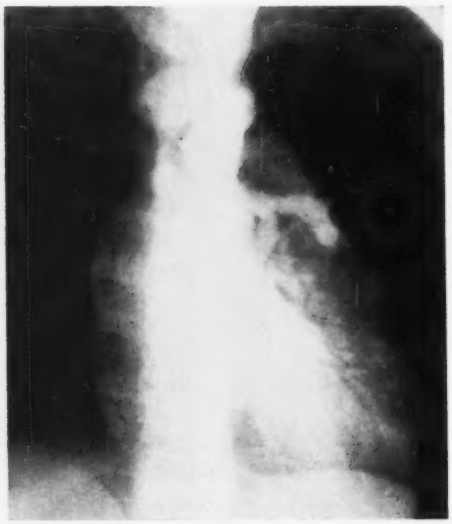


FIG. 4. Pressure recording made in patient E.B. as a catheter was withdrawn from the left ventricle (*LV*) into the aortic arch. The intraaortic pressure gradient is shown. The femoral artery pressure (*FA*) is also indicated.



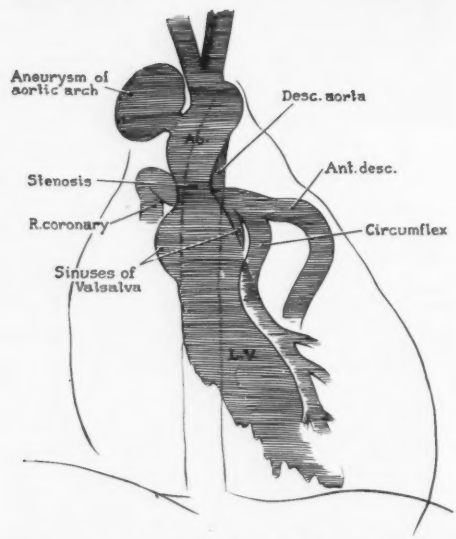


FIG. 5. Antero-posterior view of the left ventricular selective angiocardiogram (*top*) and its schematic interpretation (*bottom*) in patient E.B. The left ventricle is enlarged and its wall is greatly thickened. Both coronary arteries are grossly dilated. The aortic constriction immediately above the normal sinuses of Valsalva is indicated. The saccular aneurysm at the origin of the innominate artery is also opacified.

output at this time was 6.50 L. per minute (indicator-dilution method) and the calculated area of the stenotic orifice was 0.48 cm.^{2}/M.^{2} body surface area.

Because of the difference in blood pressure between the right and left arms the left ventricle and aorta were catheterized from the right radial artery. On this occasion, under general anesthesia, the left ventricular pressure was 180/12 mm. Hg and, as the catheter was withdrawn, progressively lower aortic pressures were recorded (fig. 4). Immediately distal to the valve it was 180/75 mm. Hg, and in the aortic arch the pressure was 120/75 mm. Hg. The femoral artery pressure was 110/75. The pressure tracings were considered diagnostic of supravalvular aortic stenosis, and to characterize the lesion further the catheter was replaced in the left ventricle and a selective angiocardiogram carried out: 50 ml. of 70 per cent Urokon were injected with a Gidlund syringe and anteroposterior and lateral films were simultaneously exposed at the rate of 6 per second (figs. 5 and 6). These demonstrated the left ventricle to be large and thick-walled. The aortic leaflets were normal in position and mobility. Immediately above the valve there was an apparently discrete narrowing of the aortic root. The sinuses of Valsalva were somewhat enlarged and all branches of both coronary arteries were enormously dilated and tortuous. The ascending aorta itself was small and a saccular aneurysm was seen to fill from the aorta near the origin of the innominate artery. The lateral views (fig. 6) also demonstrated some reduction in the lumen of the transverse portion of the aortic arch.

Operation for relief of the supraventricular obstruction was recommended but deferred for 1 year at the patient's request. He was readmitted in July 1958 at which time physical and laboratory findings were unchanged. At operation (July 17, 1958) the aorta was found to be small and there was an intense systolic thrill palpable within it. The huge coronary arteries were again noted. The aortic root was dissected and, after the institution of cardiopulmonary bypass and elective cardiac arrest, the aorta was widely opened. The site of stenosis was a thick fibrous ridge and local resection was deemed impossible. The lumen of the aorta at the site of constriction was enlarged by the insertion of a diamond-shaped prosthesis of compressed polyvinyl sponge. After 67 minutes coronary perfusion was restored but an effective heart beat never resulted.

Pathologic Description. The heart was greatly enlarged, weighing 850 Gm., and there was a 2.5-cm. calcified saccular aneurysm arising from the ascending aorta near the origin of the innominate artery. The entire aorta was hypoplastic and was only 12 mm. in outside diameter. The coronary arteries were enormously dilated and tortuous; the right was 10 mm. in diameter and the left 7 mm.

In figure 7 the aorta has been opened to show the stenotic segment, 18 mm. long, immediately above the upper margin of the aortic valve. The polyvinyl prosthesis lay in the position shown and the diameter of this stenotic segment, including the prosthesis, was only 9 mm. The aortic valve leaflets were thin and saccular and their free margins at the commissures were elongated so that the margins of the leaflets lay 4 mm. below the orifices of the coronary arteries.

Just above the orifice of the saccular aneurysm was a healed dissecting aneurysm that reentered the aorta just beyond the origin of the left subclavian artery.

Histologic sections of the aorta revealed degeneration and fibrosis of the media. These changes were particularly pronounced in the thickened stenotic segment of the ascending aorta (fig. 8).

3. J. J., a 7-year-old boy was admitted to the National Heart Institute in August 1958. A murmur had been first noted shortly after his birth. He had been asymptomatic except for slight fatigability. The child exhibited normal development and the significant physical findings were limited to the cardiovascular system. The blood pressure was 94/70, the peripheral pulses were normal. The heart was not enlarged but a ventricular lift was palpable at the apex. There was a coarse systolic thrill over the base of the heart which was also felt in the suprasternal notch and over the carotid arteries. A grade-V/VI ejection-type murmur was maximal in the second and third right intercostal spaces and was referred to the neck. The second heart sound was inaudible at the aortic area.

The electrocardiogram demonstrated left ventricular hypertrophy, and this finding was confirmed by the fluoroscopic and radiographic appearance of the heart. Poststenotic dilatation of the aorta was not apparent. At right heart catheterization the pulmonary artery pressure was 20/6 mm. Hg and the pulmonary artery nitrous oxide index was 3 per cent. Percutaneous puncture of the left ventricle was performed and the left ventricular pressure was 170/5 mm. Hg. The femoral arterial pressure was 110/65 mm. Hg and the peak systolic gradient was 60 mm. Hg (general anesthesia).

These findings were confirmatory of congenital aortic stenosis and operation was carried out in October 1958. At thoracotomy the entire ascending aorta was small and an intense systolic thrill was palpable within it. All the visible coronary arteries were greatly enlarged and tortuous. When the aortic root was dissected, a constriction immediately distal to the sinuses of Valsalva was apparent (fig. 9). No thrill was felt in the sinuses themselves, which were of normal size. A cathe-

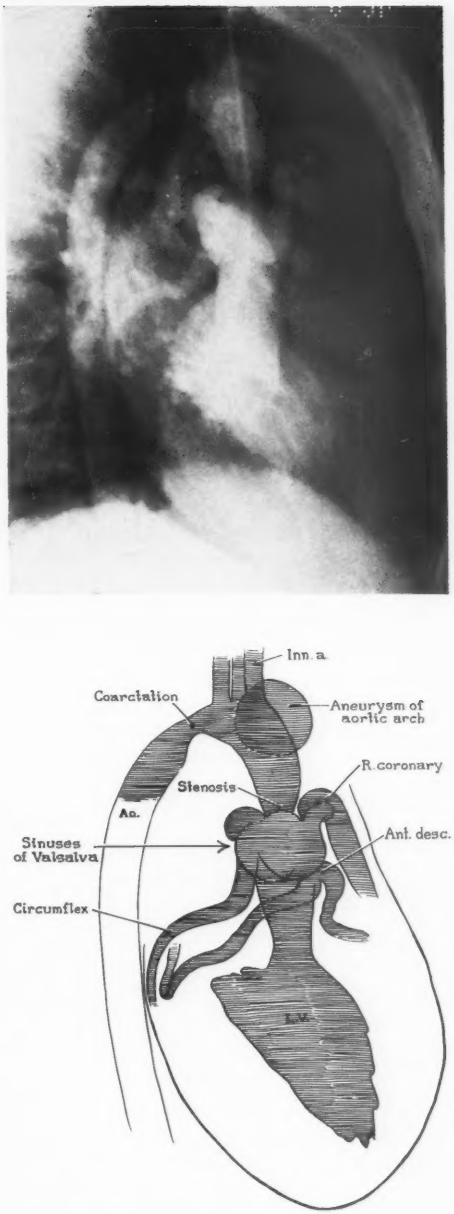


FIG. 6. Lateral view of the left ventricular selective angiocardiogram (*top*) and its interpretation (*bottom*) in patient E.B. The supravalvular stenosis, dilated coronary arteries, and the aortic aneurysm are seen. The small size of the aorta itself is also well demonstrated.

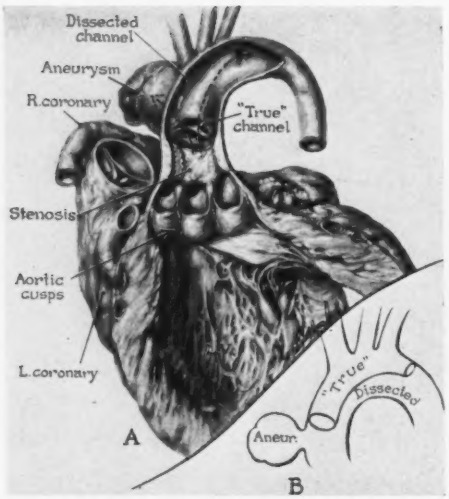


FIG. 7. Postmortem appearance of the heart and aorta of patient E.B. The stenotic segment of aorta and the prosthesis employed to enlarge the area are shown. The saccular aneurysm of the aorta and the dissection associated with it are also indicated.

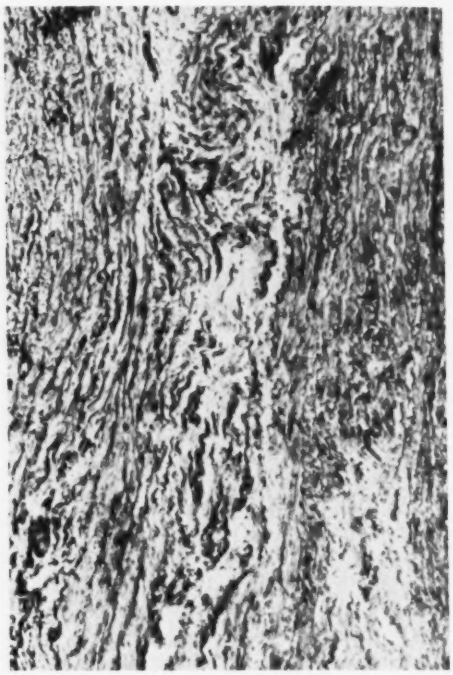


FIG. 8. Photomicrograph of the stenotic segment of aorta of patient E.B. There is separation and fraying of elastic fibers and vascularization and fibrosis in the media. Orecin-hematoxylin, × 260.

ter was passed from the apex of the left ventricle into the aorta and the withdrawal tracing proved the presence of obstruction immediately distal to the valve (fig. 10). An attempt at surgical correction of the lesion was deemed inadvisable. The child remains essentially asymptomatic.

DISCUSSION

Supravalvular aortic stenosis has been described only rarely but in the recent report by Denie and Verheugt[9] a review of cases previously described is included. The most common anatomic lesion is apparently a shelf-like thickening and hypertrophy of the plica at the upper margin of the sinuses of Valsalva. This type of stenosis may be associated with a valvular deformity as in patient J.R. The fibrous bands that extended from the free margin of each aortic leaflet to the thickened plica were in this instance apparently responsible for associated aortic regurgitation. The morphology of the valve deformity in patient J.R. suggests that the hollowing of the endocardial cushions was defectively performed and that the hypertrophied plica may have been similarly derived. In the patient reported by Denie[9] the free margin of the left coronary leaflet was fused to the aortic wall. The operative appearance of the lesion of patient J.J. suggested that it was of a similar type.

The anatomic lesion of patient E.B. is probably not embryologically similar to the stenosis described above. The stenotic segment was relatively long and was associated with hypoplasia of the aorta as well as degeneration and fibrosis of the aortic media. The history of endocarditis suggests this as an etiologic agent although the infection could have and probably did originate on a previously existing congenital stenosis. The fact that the entire aorta was hypoplastic in this, as well as the other patients, would substantiate congenital narrowing as the basic lesion.

A third type of lesion that may produce supravalvular stenosis was described by

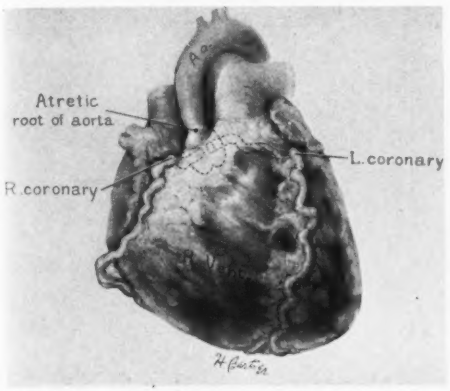


FIG. 9. Operative appearance of the heart and aorta of patient J.J. The characteristic hypoplasia of the aorta, and dilated coronary arteries are well demonstrated. The site of supravalvular obstruction is indicated.

Cheu, Fiese, and Hatayama.[10] This patient had a crescent-shaped fibrous membrane that encircled three fourths of the circumference of the lumen of the aorta and projected 1.2 cm. into the lumen. Two normal aortic valve cusps were attached to the membrane. Anomalous supravalvular aortic bands have been described and are included in the tabulation of Denie and Verheugt.[1] In spite of their speculative interest or possible embryologic relationship to anomalous valve development, clinical disease has not been evident in reported patients and the lesion has generally been an incidental autopsy finding.

On clinical examination the only finding that may serve to suggest the diagnosis of supravalvular aortic stenosis is the absence of poststenotic dilatation of the aorta. Since the aorta may not be dilated when subvalvular or functional stenosis exists,[2, 3] the presence of supravalvular obstruction can be proved only by left heart catheterization or contrast radiography. The demonstration of a systolic pressure gradient within the aortic root clearly localizes the site of obstruction to a point distal to the valve (figs. 4 and 10). Left ventricular selective angiography and aortography proved the presence of the lesion in the 2 patients in whom contrast

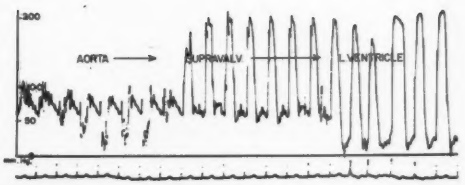


FIG. 10. Pressure recording obtained at operation in patient J.J. The intraaortic pressure gradient is clearly shown.

studies were carried out. The mere demonstration of a systolic pressure difference between the left ventricle and aorta does not localize the obstruction. Complete left heart catheterization is therefore necessary in the precise preoperative evaluation of any patient with congenital aortic stenosis.

Supravalvular aortic stenosis would seem to carry with it the relatively grave prognosis associated with the more common forms of obstruction to left ventricular outflow. Although the coronary arteries originate below the stenosis and are subjected to an abnormally high perfusion pressure, the additional coronary flow provided apparently does not compensate for the increased burden imposed upon the left ventricle. When the leaflets are fused to the aorta, the entrances to the sinuses of Valsalva may be obstructed and compromise coronary filling.

The method of surgical treatment employed in patient E.B. and contemplated in patient J.R. was suggested by Dr. John W. Kirklin.[11] He emphasized that excision of the obstructing ridge would necessitate severance of the attachments of the aortic leaflets and would certainly result in gross aortic regurgitation. The accuracy of this observation is shown by the relationships of the leaflets to the obstruction in figures 2 and 7. Kirklin successfully enlarged the diameter of the aortic root by the insertion of a diamond-shaped polyvinyl patch in a patient in whom the anatomic lesion was similar to those described. A significant reduction in the intraaortic pressure gradient was achieved and it would seem that this method of operative repair will find increasing application.

Summary

The clinical and hemodynamic findings in 3 patients with supravalvular aortic stenosis are described. The diagnosis was established by left heart catheterization and selective angiography. Two patients died, one following an unsuccessful attempt at surgical correction of the lesion. Pathologic findings in these patients indicate that the stenosis, which occurs at the site of insertion of the aortic leaflets, is of congenital origin. The differentiation of this lesion from the more common forms of aortic stenosis and the problem of its surgical management are described.

Summario in Interlingua

Es describite le constatationes clinic e hemodynamic in 3 patientes con stenosis aortic supravalvular. Le diagnose esseva establite per catheterismo sinistro-cardiac e angiographia selective. Duo del patientes moriva, le un post le van essayo de corriger le lesion per medios chirurgic. Le constatationes pathologic in iste patientes indica que le stenosis, que occurre al sito del insertion del cuspides aortic, es de origine congenite. Le differentiation de iste lesion ab le formas plus commun de stenosis aortic e le problema de su tractamento chirurgic es describite.

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Lipoproteins, Cholesterol and Serum Proteins as Predictors of Myocardial Infarction

By IRVINE H. PAGE, M.D., AND LENA A. LEWIS, PH.D.

The normal variability of lipoprotein and cholesterol levels was established for 6 women over a period of 5 months for comparison with levels in people who develop myocardial infarction. We have studied 107 normal men for 7 years. Among these 11 developed infarction and 6 angina pectoris. Little change in lipid levels was associated with these events. Electrophoretic patterns early after infarction showed certain relatively characteristic changes, especially increase in α-2 and β globulins and fibrinogen. Low-density lipoprotein also increased. While α-2 globulin was usually greatest in patients with the most extensive myocardial damage, there was little over-all correlation between lipoprotein pattern and severity of infarction. The "coronary profile" can be more sharply delineated by repeated lipid measurements because as a group those with atherosclerosis and infarction exhibit slightly elevated values.

ONE of the most persistent problems in cardiology is inability to diagnose coronary atherosclerosis until manifestations of myocardial ischemia appear and to predict the likelihood of myocardial infarction. The two may under some circumstances be separate problems but, surely, they are usually closely intertwined. The finding that cholesterol levels were raised in some patients after infarction and that infarction was more common in patients with persistent hypercholesterolemia suggested that measurement of this plasma constituent might have prognostic value. This has been shown to be true[1, 2] on a statistical basis but alone is often too unreliable for individual forecasting.

When Gofman et al.[3] showed significant elevation of lipoproteins 3 or more months after infarction and indicated a much higher accuracy of prediction using either lipoproteins or an "atherogenic index" compounded of other variables, hope was high that the problem of the individual suspect of coronary disease might be solved. This hope proved to be illusory in that the lipoprotein measurements were no better than cholesterol.[4] Gofman's major contribution was in calling attention to the great importance of lipoproteins in relationship to the mechanisms of atherogenesis. It is currently well recognized that most of the lipid in the blood is in the form of lipoprotein and that the β-lipoproteins are the ones most actively concerned with atherogenesis.

But there have been persistent doubts about these conclusions[5] because most of the studies have been concerned with the lipid levels after, rather than before, infarction. So many changes in diet and living habits occur as a result of severe illness that the doubts may be justified. For this reason we have examined the serum protein and lipid patterns before and after the infarction in the same patients. In this way a longitudinal or "cohort" study has been done instead of the usual cross-sectional one.

The Gofman ultracentrifuge technic has been modified by raising the specific gravity of serum from 1.063 to 1.21 with potassium bromide.[6] The α-lipoproteins, the most dense of the lipid fractions, are then floated with the less dense lipoproteins, and permit more complete recovery of the S_f 1-3 fraction. The α_2-lipoproteins ($-S_{1.21}$ 20-25, i.e., S_f 1-3) are only partially resolved at the lower serum density used by Gofman and the $-S$ (1-10) are not resolved at all. In addition to somewhat the same information obtained at density

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1.063, the −S 1-10 and 20-25 lipoproteins are clearly defined as well. The change in density requires a change in nomenclature:

$-S_{1.21}$	$S_{f1.06}$	Electrophoresis
70-400	20-100*	$\beta + \gamma_1$ globulin
40-70	12-20	slow α_2 or fast β†
25-40	3-8	β
20-25	1-3	α_2
10-20*	—	—
1-10	—	α_1

*No measurable material normally present.
†Mobility of −S 40-70 fraction varies, usually migrates as α_2 to fast β; may occasionally migrate as γ_1.

The well known S_f 12-20 fraction of Gofman corresponds to −S 40-70 at the increased density. Negative sedimentation or flotation is designated by the symbol −S in our nomenclature.

Method

The electrophoretic pattern of the plasma proteins was studied by Longsworth's modification of Tiselius' method with use of phosphate buffer pH 7.8 and ionic strength 0.16 μ.[7] Serum cholesterol was measured by the method of Abell, Levy, Brodie, and Kendall.[8] Blood samples were drawn before breakfast. When sufficient serum was available, measurement of lipoproteins was made at more than one concentration to obtain clearer resolution.

Samples of blood were obtained in 84 patients as soon as possible after myocardial infarction. Studies were repeated at intervals of 5 to 10 days on 66. Four of the patients were studied at similar intervals after a second infarction. Twenty-five subjects were studied 3 months or more after infarction.

Samples of serum of 107 normal men collected as described in detail in the cooperative lipoprotein study sponsored by the U. S. Public Health Service were analyzed at a density of 1.063.[4] Studies were made yearly on each for 5 to 7 years. In 11 of the subjects who suffered myocardial infarction and 6 with angina pectoris or coronary insufficiency, lipoprotein studies were obtained after, as well as before, the development of symptoms of atherosclerosis.

Results

Watkin, Lawry, Mann, and Halperin[9] found that the serum lipoprotein pattern of normal persons measured at d 1.063 by ultracentrifugation usually varied relatively little. This is such an important facet that we examined the ultracentrifuge pattern at d 1.21 of 6 normal women aged 20 to 50 years at weekly intervals for about 5 months. Use of the higher density reveals the −S 1-10 fraction not seen at d 1.063.

Our results showed that the degree of stability was highly dependent on the specific lipoprotein fraction (fig. 1). The −S 1-10 showed wide variations in sharp contrast to −S 40-70. The −S 70-400 was likely to exhibit unexpected and not easily explicable peaks. These variations are not so apparent in the tabular data of the means (table 1). Clearly, these data show the danger of accepting a single determination of lipoproteins as representative of the average concentration. We believe, however, that the alterations described here as occurring following myocardial infarction are beyond these limits of natural variation.

Weekly measurement of serum cholesterol in 5 young women showed stability, especially when the average level was low. Above levels of about 260 mg. per 100 ml. the variation became large (fig. 2).

The changes in lipoproteins and serum proteins found 1 to 4 days after infarction were highly variable. The majority, i.e., 44 of the 66, showed increase in −S 20-25 and moderate elevation of α_2- and Φ-globulin (table 2). Another 15 of the 66 exhibited increase in low-density lipoprotein (−S 40-70 and −S 70-400) along with similar change in serum protein (subject "G," table 2 and "L," table 3, for example). Finally 7 of the 66 had marked changes consisting of a progressive rise in the following 2 to 3 weeks in low-density lipoproteins and a double peak appearing in the −S 25-40 competent. α_2- and β-globulin in these increased greatly; there was some elevation of Φ-globulin. Poor resolution of α_2- and β-globulin was noted concurrent with lack of resolution of the −S 20-40 component.

The level of serum cholesterol in the male patients after myocardial infarction was highest in the younger age group (25 to 35 years) and lowest in the oldest group (over 65 years).

TABLE 1.—*Stability of Serum Lipoproteins of Normal Women*

Subject	Serum lipoprotein (mg. per 100 ml. serum)					Cholesterol	No. of determinations
	—S 70-400	40-70	25-40	20-25	1-10		
-C	13.9±2.1*	21.7±1.9	191.6±5.4	15.0±1.6	192.6±5.5	209.5±1.7	14
-C	7.9±1.9	13.1±1.3	148.6±5.3	23.2±2.2	261.9±9.9	200.6±3.8	11
-C	19.8±1.7	26.7±1.2	>250	19.6±1.2	252.2±8.2	270.8±7.7	22
-C	13.5±1.8	21.3±1.5	169.0±4.7	18.0±0.9	260.0±6.2	189.0±7.5	27
-C	13.1±1.6	18.5±1.4	127.3±12.4	18.1±0.8	206.2±5.8	135.5±1.3	26
V-C	6.2±1.4	19.8±1.4	>250	19.9±1.1	364.0±9.3	248.3±10.9	24

*Mean ± S.E. mean.

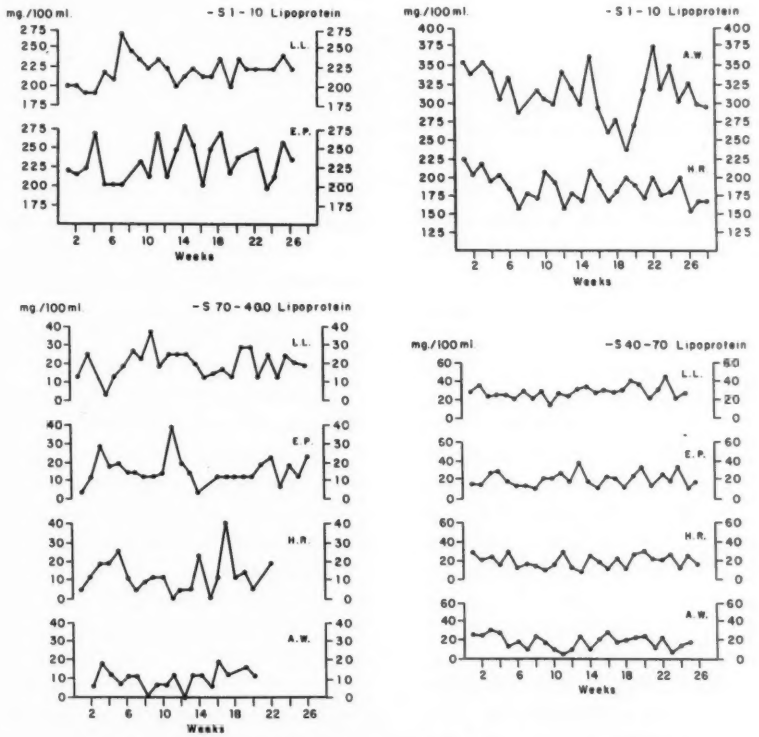

FIG. 1. Fluctuation of serum lipoprotein values of normal women.

In the small female group no such trend in cholesterol concentration with age was evident (table 3).

Four subjects had a second myocardial infarction (table 4). The concentration of —S 70-400 and —S 40-70 increased after both infarctions. In 2 of the patients the —S 25-40 fraction showed a double peak with maximum deflection at —S 27 and 33. Similar changes were noted after both infarctions. In subject "R," —S 20-25 showed greatly increased concentrations at 14 days, and at 21 days the resolution of this component from the —S 25-40 fraction was obscured.

The serum cholesterol concentration increased between the second and fourteenth

TABLE 2.—*Examples of Serum Lipoprotein Patterns Shortly after Myocardial Infarction*

Subject	Age (yr.)	Sex	Days after myocardial infarction	Serum Lipoproteins —S 70-400	40-70	25-40 (mg. per 100 ml. serum)	20-25	1-10	Cholesterol
R	46	M	2	29	69	>229	14	170	275
			14	182	88	104(32)*	>182(26)*	108	313
			21	104	94	>260		165	328
G	55	M	3	91	47	>200	16	200	—
			11	78	31	>200	18	145	—
			18	39	70	>250	10	145	—
			48	56	70	351	8	210	—
D	58	M	1	24	40	366	19	140	255
			9	28	47	378	28	142	273
			17	50	30	>260	38	120	260
Normal mean± S.E.	38-60	M		60±10.0	35±1.0	285±17	14±0.9	180±5.1	232±7.8

*—S value of maximum point of deflection of peak.

day after infarction in 2, while less marked shifts were noted in the other subjects. The β-globulin was somewhat elevated at the time of the first study after infarction. It was even higher 2 to 3 weeks later. This is in contrast with the α_2-globulin in which the greatest increase was usually observed at the time of the first determination after infarction. The albumin, which was low initially, tended to return toward normal within 3 weeks. There was no significant change in γ-globulin concentration during the early postinfarction period. The plasma electrophoretic and lipoprotein changes after each of the 2 infarctions were strikingly similar, i.e., α_2-globulin was very high at the time of the initial study while β-globulin increased over longer periods.

It was of special interest because of the belief that the ratio of α- to β-lipoprotein is a determinant in atherogenesis to find that the α_1-lipoprotein (−S 1-10) was not constantly modified. There was a decrease of about 35 per cent in one fifth of the patients 15 days after infarction, no change in 62 per cent, and an increase of 35 per cent in another fifth of the patients. These changes bore no relationship to the type of lipoprotein change discussed above.

There was little correlation between the lipoprotein pattern and the severity of the infarction as judged by reading of the electrocardiograms and the clinical evidence (table 5). While there was not always good correlation between the electrophoretic serum protein pattern and clinical course, the increase in α_2-globulin was usually greatest in the patients with most extensive cardiac damage (patient DE, table 5) and least in those with minimal damage (patient WE, table 5).

Lipoprotein Patterns Late after Recovery from Myocardial Infarction. The lipoprotein patterns obtained on 25 patients (33 to 72 years of age) 3 months to 10 years after myocardial infarction showed a wide range of concentration in all fractions. Eighteen showed a level of −S 1-10 lower than the mean control value for normals of the same age and sex. Unlike the levels soon after infarction, the −S 20-25 concentration was significantly elevated in only 2 patients. The −S 40-70 ranged from 8 to 100 mg. per 100 ml., 7 of the 25 falling above the level of 75 per cent of the normal population. The −S 70-400 ranged from 13 to 160, 5 of 25 falling above the level of 75 per cent of the normals.

Electrophoretic study of the plasma proteins of 20 of the patients showed comparatively small changes from the normal concentrations. The most striking alteration was elevation of β-globulin. Fourteen had

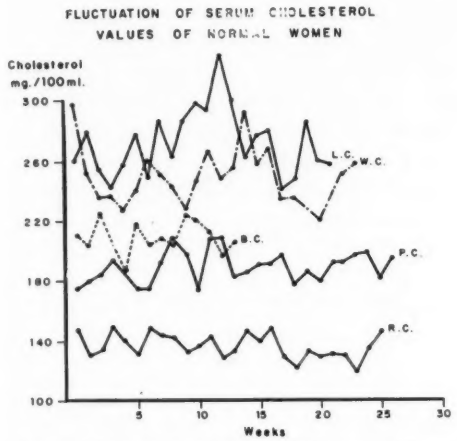

FIG. 2. Fluctuation of serum cholesterol values of normal women.

values above the normal mean of 1.11 ± 0.03 Gm. per 100 ml. Six of the 14 had values of 1.5 Gm. per 100 ml. or greater.

Studies Made before and after Myocardial Infarction. The lipoprotein patterns were studied in 107 "normal" Cleveland executives who had annual studies of their lipoproteins at d 1.063 for periods up to 7 years. Twelve of these subsequently suffered infarction while 6 developed angina pectoris or coronary insufficiency as determined electrocardiographically. The lipoprotein studies were repeated on them and, since the period was relatively long after infarction (at least 2 months), it was hoped to avoid the effects of those immediate changes inevitably resulting from so serious an episode.

Impressive is the lack of change; both lipoproteins and total cholesterol remained about the same. When weight loss was large, as, for example, in N-7, fall was noted as was to be expected. In one patient (N-11) a low-fat diet was taken, and this may have been responsible for somewhat lower lipid levels. Two of the patients (N-4 and N-8) received heparin regularly after infarction but this did not produce significant changes in plasma lipids.

Of the 18 who developed infarction or angina 5 had S_f 12-20 values greater than

TABLE 3.—*Relation of Serum Cholesterol to Age in Patients Soon After Myocardial Infarction*

Age range, years	25-35	36-45	46-55	56-65	>66
No. of male patients	2	11	20	15	14
Serum cholesterol mg./100 ml.*	444	265	251	239	196
No. of female patients	0	1	2	4	7
Serum cholesterol mg./100 ml.		212	278	330	268

*Average of values obtained 2-12 days after myocardial infarction.

75 per cent of the normals, and 5 had S_f 20-100 values greater than the 75 percentile level, the level below which 75 per cent of the normal population falls.[4] Of 12 subjects who had cholesterol studies before the appearance of overt coronary disease, 3 had values above the 75 percentile level of normal subjects.

DISCUSSION

The profile of the patient who is developing coronary atherosclerosis is currently only dimly discernible. Family history of vascular disease, mesomorphic physique, persistent elevation of plasma lipids and uric acid, slight elevation of arterial pressure, and possibly obesity make up the usual picture. Nonspecific abnormalities of the electrocardiographic waves are believed to have some prognostic value according to Doyle et al.[10] These, plus the heavy consumption of fat, tobacco, and alcohol are factors thought to add accuracy to prognosis. The fact that there are so many components suggests a lack of specificity of any one. Indeed, it is not at all improbable that there is no specific determinant of atherogenesis, hence the profile will be reflected in the mathematical relationship among a variety of factors. There is wide division of opinion as to the significance of stress. There may even be several groups of individuals prone to coronary disease[11-13] differing in the totality of their several characteristics.

The closely associated problem of myocardial infarction has still other and not neces-

TABLE 4.—*Comparison of Electrophoretic and Ultracentrifuge Patterns after Repeated Myocardial Infarction*

Subject	Sex	Days after infaret	Serum lipoproteins (mg./100 ml. serum) —S 70-400	40-70	25-40	20-25	1-10	Cholesterol (mg./100 ml. serum)	Plasma proteins (Gm./100 ml. plasma) Tot. protein	Alb.	+1	2	β	γ	φ	Special notes
R	M	2	29	69	>229	14	170	275	6.99	3.27	1.38		1.10	0.60	0.64	
		14	182	88	104(32)	>182(26)	108	313	6.58	3.01	1.33		1.27	0.62	0.35	
		21	104	94	>260*		165	328	7.38	3.70	1.21		1.37	0.69	0.41	
		90	33	47	>223	9	83	281	7.22	4.26	0.77		1.11	0.74	0.34	
		136†														
		138	50	59	>237	14	98	285	8.03	3.96	1.53		1.57	0.97	serum	
		145	85	95	>284‡	‡	101	330	8.13	4.30	1.06		1.86	0.90	serum	
		416	84	26	285*		169	267	8.00	5.16	0.83		1.04	0.54	0.43	
L	M	7	107	38	175	5	163	197	6.60	3.19	0.94		1.13	0.74	0.60	
		21	52	52	>142	16	127	245	7.35	3.74	0.67		1.53	0.90	0.51	
		187†														
		191	49	52	188	9	167	208	7.00	3.62	0.40		1.52	0.96	0.50	
		198	54	47	>188	21	108	225	7.00	3.40	0.90		1.31	0.84	0.55	
		204	67	67	>200	17	127	251	7.00	3.84	0.97		1.10	0.70	0.59	
K	M	4	26	26	234	26	94									
		12	26	31	>200	18	125									
		20	65	39	170‡	26	140									
		123†														
		128	38	19	>200	24	118	258	6.30	3.46	0.65		1.27	0.49	0.43	
		137	47	45	>200	38	170	264								
		143	47	43	>250‡	50	170	252	6.72	3.84	0.54		1.42	0.43	0.49	
M	M	12	50§	43	>200			429	6.68	3.38	0.64		1.36	0.79	0.51	diabetic
		19	65§	52	>200			453	6.97	3.88	0.58		1.69	0.82	serum	
		66	80§	33	>200			—	7.09	4.14	0.58		1.58	0.79	serum	
		120	72§	30	>200			354	6.46	3.74	0.52		1.20	0.68	0.32	
		194†														Started low-fat diet: C 220, P 85, F 14
		196	—§	21	>200			350	6.78	3.68	0.53		1.31	0.59	0.47	
		220	45§	51	>200			—	7.84	4.52	0.67		1.75	0.90	serum	
		1006	38	30	>188	38	242	225	8.65	4.82	0.72		1.57	0.99	0.55	
		1481	28	33	>188	12	272	228	7.20	3.74	0.53		1.39	0.93	0.61	

*—S 20-40, —S 20-25 not resolved from —S 25-40.

†Second myocardial infarction.

‡Double peak.

§Determined at d 1.063. S_f 12-20 equivalent to —S 40-70. S_f 20-100 equivalent to —S 70-400.

sarily related facets. It is well recognized that coronary atherosclerosis leads to thrombosis in a capricious fashion and that thrombosis can occur rarely in its absence. The clinical picture is even further complicated by the fact that thrombosis is not a necessary precedent to myocardial infarction. Having said this we must, however, proceed with our investigation under oversimplified terms. This we fully confess.

Our results, along with those of Watkin, Lawry, Mann, and Halperin,[9] who also made serial lipoprotein determinations at a different density on normal subjects, show that they exhibit sufficiently stable lipoprotein and protein patterns to make cautious comparison with patterns over a period of months or years. Our results, however, show that stability depends much on the fraction of lipoproteins examined. The −S 40-70 are stable and the −S 70-400 and −S 1-10 relatively unstable.

Even when laboratory error is largely eliminated, serum cholesterol values still show considerable variability. While fasting values are a little less variable, meals do not greatly affect cholesterol levels. Cholesterol values tend to rise with age as measured in a population[14–16] but it has now been repeatedly shown that this need not be true in all healthy individuals.[17–19] Unfortunately, the notion is now firmly fixed, due merely to repetition, that cholesterol always rises with age.

There is some disagreement as to the normal variability of cholesterol levels in the same individual. Thomas and Eisenberg[20] have presented both an excellent study and a literature survey of the problem. They found 92 per cent of the initial values of medical students lay between 150 and 299 mg. per cent, with a mean of 229 mg. There was a wide range of values, but over periods of months or even years there was relative stability.

Against the view that there is relative constancy of cholesterol levels in individuals is recent work showing that stresses of all sorts

TABLE 5.—*Relationship of Severity of Myocardial Lesion to Serum Lipoprotein and Electrophoretic Protein Patterns*

Subject	Sex	Age	Days after infarct	Location and size of infarct	Course	Serum lipoproteins (mg./100 ml. serum)					Cholesterol	Electrophoretic protein pattern (Gm./100 ml.)			
						−S 70-400	40-70	25-40	20-25	1-10		T.P.	A.	α_2	β	γ
DE	M	62	5	Large anteroseptal	Uneventful, no angina	10	63	264	10	113	219	6.11	3.28	0.80	1.38	0.65
JA	F	40	7	Moderate posterior	Some pain for few days in hospital	56	62	252	39	111	256	—	—	—	—	—
SE	M	46	6	Moderate to large anteroseptal and anterior	Coronary pain in hospital, extension of infarct 13th day	21	62	260	18	191	206	7.85	4.21	0.82	1.41	1.41
WE	M	69	10	Small posterior, no QRS changes	Uneventful, no angina	35	68	>235	41	84	318	7.09	4.31	0.53	1.50	0.75
Normal men		35-60	Mean± S.E.			60± 10.0	33± 1.0	285± 16.9	14± 0.6	180± 4.6	232± 7.9	7.44± 0.15*	4.74± 0.11*	0.54± 0.04*	1.11± 0.03*	1.04± 0.05

*Mean±S.D.

TABLE 6.—*Serum Lipoproteins, Determined at d 1.063, of Male Executive Group before and, When Possible, after Development of Myocardial Infarction*

Subject	Date	Body wt. (lb.)	S_f 12-20 (mg./100 ml. serum)	20-100 (mg./100 ml. serum)	Cholest. (mg./100 ml. serum)	Date of infarction or beginning vascular complication	Time after first study in months*
N-1	2/27/51	153	53	75	—	3/10/53	25
	2/26/52	155	13	99	166	coronary insufficiency	
	2/17/53	152	30	43	273		
	2/16/54	150	42	71	261		
	1/16/56	153	14	40	288		
	4/19/58	152	32	93	230		
N-2	3/6/52	165	17	71	161	5/10/52	2
	3/4/53	177	47	82	210	angina pectoris began	
	4/13/54	170	42	52	211		
	6/16/55	170	8	24	189		
	8/27/57	170	32	32	195		
N-3	2/14/52	171	29	74	309	9/24/57	67
	2/10/53	176	34	75	291	posterior myocardial infarction,	
	2/14/55	182	28	96	302	10/28/57—died	
	2/9/56	182	13	39	285		
N-4	1/29/52	172	57	88	350	1/5/53	12
	1/23/53	165	28	54	343	angina pectoris	
	10/29/57	160	39	77	272		
N-5	3/6/50	180	26	70	—	5/7/50	2
	10/9/50	176	27	60	263	myocardial infarction	
	3/25/53	—	54	152	270		
N-6	3/30/51	196	33	69	—	9/15/51	6
	3/26/52	202	57	63	337	posterior myocardial infarction	
	3/9/55	209	16	54	270		
	3/7/56	207	36	54	205		
	3/20/57	207	30	20	282		
	3/17/58	205	20	46	258		
N-7	6/22/51	240	70	160	—	11/21/52	18
	6/20/52	234	57	170	264	posterior myocardial infarction	
	6/17/53	198	45	39	189		
	1/17/56	204	40	28	223		
	1/17/57	213	42	140	189		
	2/12/59	206	88	140	239		
N-8	2/2/53	200	22	106	270	2/1/55	24
	2/2/54	198	47	75	270	angina pectoris developed, taking	
	2/10/55	180	24	94	280	200 mg. heparin q. weekly	
	2/14/56	182	56	53	270		
	2/19/57	180	13	45	271		
N-9	2/21/51	174	53	270	—	2/17/52	12
	6/13/52	175	56	105	243	myocardial infarction, died	
	6/19/53	177	75	165	260	following acute myocardial	
	6/3/54	182	87	251	218	infarction 3/6/58	
	6/3/55	180	94	424	264		
	6/26/56	180	56	300	242		

(*Continued on next page*)

TABLE 6.—*Continued*

Subject	Date	Body wt. (lb.)	S_f 12-20	20-100	Cholest.	Date of infarction or beginning vascular complication	Time after first study in months*
			(mg./100 ml. serum)				
N-10	1/23/51	189	65	92	—	10/24/51 myocardial infarction, 1/20/55 died, heart failure	9
N-11	9/15/52	191	11	78	250	7/7/55 massive anterior myocardial infaret, on low cholesterol diet since 1955	34
	6/14/53	190	17	71	212		
	10/5/54	195	18	62	230		
	6/22/56	185	7	49	195		
	6/24/57	185	26	20	218		
N-12	4/30/51	145	16	42	—	3/20/53 myocardial infarction	23
	4/28/52	151	13	32	268		
	3/9/53	149	16	52	233		
	8/18/53	138	24	34	250		
	3/12/54	137	29	15	237		
	3/1/55	140	6	30	240		
	2/1/56	140	10	12	245		
	1/11/57	135	11	25	231		
	1/7/58	140	12	8	194		
N-13	5/10/51	198	51	138	—	1/30/55 angina pectoris	44
	5/28/52	201	25	44	250		
	6/1/53	194	35	81	242		
	5/19/54	195	37	77	247		
	5/5/55	192	32	58	238		
	5/2/56	191	49	76	274		
	6/3/57	195	62	108	274		
	6/30/58	194	120	101	265		
N-14	4/19/51	185	33	125	—	3/30/52 posterior myocardial infarction	11
	4/3/53	175	45	160	265		
N-15	10/6/50	180	34	70	—	7/1/52 acute myocardial infarction	22
	9/4/51	176	8	39	260		
	8/6/52	180	9	26	242		
N-16	4/12/51	220	61	172	—	6/23/51 died following myocardial infarction	2
N-17	10/2/51	177	25	60	217	12/1/58 angina pectoris	84
	6/24/53	174	47	86	204		
	6/1/54	165	36	22	196		
	4/13/55	177	38	54	218		
	11/11/56	172	18	120	—		
	4/5/57	176	40	72	205		
	9/16/58	176	54	99	206		
	4/6/59	175	35	72	183		
N-18	5/24/51	144	33	66	—	10/10/58 myocardial infarction	77
	5/27/52	146	38	120	238		
	5/26/53	147	45	133	251		
	5/25/54	147	29	162	238		
	5/24/55	146	18	90	228		
	5/17/56	150	58	141	239		
	5/26/58	149	35	121	267		

*This represents the time in months of onset of signs of infarction or coronary insufficiency after the first blood studies were made.

either lower them,[21] raise them,[22, 23] or have no effect.[24, 25]

The serum cholesterol was carefully studied, by Hammarston, Cathey, Redmond and Wolf,[26] in 12 well-controlled subjects who had sustained myocardial infarction. No weight change or gross alteration in diet occurred. Over a 9-month period a mean decrease of 13 per cent was noted. On 20 occasions cholesterol rose higher than the mean for that individual and on 19 of these the periods were judged to be especially stressful.

Our results on normal young women showed relative stability, especially in those with lower average levels of cholesterol. But those with levels above 260 mg. per 100 ml. varied to a considerable degree. There was nothing to suggest that stress was related to these changes, if it is meant by stress some event of great emotional intensity.

We have for instance recently studied the effect of cigarette smoking on blood cholesterol levels over half-hour periods.[27] No clear effect was discernible. It is not sure in our minds that smoking is a stress though it is said to be by some.

Serum total cholesterol has been found slightly elevated in a statistically significant number of patients after infarction.[1, 2, 28, 29] But severe coronary atherosclerosis with or without myocardial infarction may occur in the absence of hypercholesterolemia, the level of cholesterol being compared with control values obtained from the adult American population. The slight lowering of lipid phosphorus in relation to cholesterol which occurs in some patients does not occur in all. As shown by Page et al.[17] when total lipid in plasma of normal persons rises, each of the 4 main constituent fractions also increases, but not to an equal extent. Free cholesterol takes the least, and neutral fat, the greatest part in the change. Phosphatides remain fairly stable throughout. If there is a significant fall in them, their usual stability might give such a reduction added significance.

The most constant change in serum protein pattern early after infarction was increase in concentration of α_2-globulin from 100 to 300 per cent above normal as also noted by others.[30-32] This fraction is a very complex one containing at least 10 components, including such diverse substances as glycoproteins, haptoglobins, and renin-substrate. It is increased in experimental hemorrhagic shock,[33] in hyperthyroidism,[34] Cushing's syndrome,[35] and certain infectious diseases[36, 37] usually in which tissue catabolism is great. During the second week an increase in β and α globulin may take place.[38]

Lewis and Page[39] first pointed out that an elevated plasma β-globulin concentration is associated with occurrence of vascular disease. Thus, elevated levels have been observed in patients with vascular disease of varied etiology as well as in myocardial infarction. While patients with mild essential hypertension usually have normal β-globulin levels, a high concentration was consistently found in patients with malignant hypertension. In diabetic subjects under good control, those without vascular complications usually had normal β-globulins, while those with diabetic retinitis or Kimmelstiel-Wilson syndrome showed elevated concentrations.[34] Frequently increase in fibrinogen was also observed after infarction. But after 3 or 4 months the pattern was usually normal except for slightly elevated β-globulin.

The change in lipoproteins elicited by the occurrence of infarction during the first 16 days in 67 per cent of our patients was limited to an increase in the −S 20-25 component. This component has the same electrophoretic mobility as α_2-globulin. In others (23 per cent) the −S 40-70 and less dense components increased. The last, and smallest group (10 per cent) showed progressive increase for 3 weeks, or more, in concentration of the fractions with flotation rate above −S 25. The −S 25-40 component often changed from a single to a double peak with maximum deflections at −S 26 and 32. There was no relationship discernible between any of these components and the severity, or position, of

TABLE 7.—*Serum Lipoprotein Pattern at Least Three Months after Myocardial Infarction*

No.	Sex	Age	Mo. after myocardial infarct.	Lipoproteins (mg./100 ml.) —S?0-400	40-70	25-40	20-25	1-10	Cholesterol	Additional notes
1X	M	55	6	>100	24	80	6	101	—	Low cholesterol diet
2X	M	58	36	35	68	>235	41	84	265	
3X	M	33	24	80	20	300	12	99	—	
4X	M	46	24	40	26	>235	—	125	—	
5X	M	38	8	13*	47	182	13	118	172	Low cholesterol diet
6X	M	55	4	42	30	260	—	91	226	Low cholesterol diet
7X	F	54	5	50	37	>250	50	170		
8X	M	50	24	30	38	>160	14	101	256	
9X	M	54	48	70	35	>200	10	198	306	Low chol.—low animal fat diet
10X	M	44	12	30	26	>235	6	165	240	
11X	M	49	5	16	8	160	8	120	170	Low fat diet
12X	M	52	3	100	28	100	6	125	—	Low fat diet
13X	M	72	6	10	28	>150	6	91	—	
14X	M	59	120	12	28	>220	4	91	—	
15X	M	53	36	60	20	>235	20	159	—	
16X	M	64	24	16	22	140	6	170	—	
17X	M	36	5	40	30	>235	6	91	—	Malignant hypertension
18X	M	46	4	40	70	180	8	80	—	
19X	M	58	12	20*	28	320	14	125	261	Low fat diet
20X	M	46	3	33	47	>235	9	79	281	
21X	M	48	6	150*	90	>350	15	254	347	Dicumarol regularly
22X	M	52	84	64	60	160	—	136	—	
23X	M	51	5	45	50	>200	12	148	208	
24X	M	64	72	64*	60	160	—	136	246	
25X	F	52	9	150	100	200	12	83	252	

*Very fast rising component —S>400 4+.

the myocardial lesions. Until more is learned about the effect of hypotension, fever, tissue necrosis, etc., during the acute episode, it will be difficult to determine which of these changes might be associated with the lipid changes occurring immediately after infarction. An increase in concentration of serum low-density lipoproteins —S 25-400, and decrease in —S 1-10 was observed in our patients receiving pyrogen injections.

The decreased albumin concentration in the early period following acute infarction may be caused, in part, by increased rate of degradation of albumin due to fever. Flick and Steinfeld[40] observed increased rates of degradation in subjects with fever induced by typhoid H antigen.

The apparent low concentration of α_1- lipoprotein in females with infarction may be exaggerated by the fact that comparison is made of largely postmenopausal with a somewhat younger premenopausal group of normal women. Such factors do not enter into the evaluation of the men. In the men there was a definite tendency for the —S 1-10 concentration to be decreased, although 6 of 22 patients studied 3 months to 10 years after occurrence of infarction had normal values.

Serum lipids were measured by Paterson, Cornish, and Armstrong[41] in 800 patients permanently confined to a hospital. In the 50 who died the total cholesterol and S_f 12-20 and S_f 20-100 fractions showed no significant relationship with the degree of atherosclerosis found at autopsy. They believe their preliminary evaluation makes a poor case for a direct relationship among certain serum lipids and atherogenesis. On the other hand, Spain. Bradess, and Greenblatt[42] found the serum β-lipoprotein pattern, the dominant somatotype, and the degree of aortic and coronary

atherosclerosis as determined at autopsy in 157 individuals to be closely correlated.

Doyle et al.[43] examined 28 survivors of myocardial infarction and found increase in lipoprotein cholesterol and phosphatide which was accounted for by an increase in the β-lipoprotein fractions. The wide overlap of values nullified the individual diagnostic value of the measurements. They concluded that presently available technics for measuring blood lipoproteins are neither qualitatively nor quantitatively satisfactory indices of atherogenicity in a homogeneous population highly susceptible to ischemic heart disease.

The proportion of a range of fatty acids from C_6 to C_{20} was examined by James et al.,[44] using gas-liquid chromatography in 12 patients with coronary artery disease and 12 matched controls. No difference was found in the proportions of any fatty acids between patients and controls. The results do not support the hypothesis that deficiency of essential fatty acids is a factor in atherogenesis.

Paper electrophoresis was used by Jencks et al.[45] in the analysis of 77 men with myocardial infarcts. A significant fall in α-lipoprotein and increase in β-lipoprotein was observed when compared with a control group. Elevation of total cholesterol was less marked. Confirming Barr[46] they found less of the total cholesterol in the α-lipoprotein during the first 6 months after infarction. Ultracentrifugal analyses of lipoproteins of the S_f 12-20 class were less often abnormal than were electrophoretic analyses of the ratio of α-lipoproteins. Chapin and Proger[47] found in patients 1 to 3 weeks after recovery from myocardial infarction on the average relatively less phosphatide in the β-lipoproteins and relatively more in the α-lipoproteins when compared with sera of young women. Since paper electrophoresis was used in both these studies, definition of the limits of error of the method is highly to be desired. So far there is no indication that the distribution of cholesterol or phosphatide between the β- and α-lipoproteins have greater predictive value than cholesterol or total lipoproteins. It also remains to be proved that these ratios truly reflect the colloid stability of the lipoproteins.

Barr, Russ, and Eder[48] and later Oliver and Boyd[49] found a tendency for an absolute and relative decrease in α-lipoproteins as measured by the Cohn fractionation method to occur in atherosclerotic patients. There was a concurrent increase in β-lipoproteins. These changes may occur in the absence of hypercholesterolemia or elevation of cholesterol/phosphatide ratio of the unfractionated plasma. Several months after myocardial infarction our patients tended toward lower than average −S 1-10 values while some had normal or even high values. A low −S 1-10 was not a consistent finding in the immediate postinfarction period although the mean value was lower than the mean for the control group. Thus, two different methods show roughly the same thing, namely that α-lipoproteins may be reduced but this is not an invariable finding in patients with myocardial infarction.

Added importance is given these findings by the demonstration[50] that estrogens promptly and consistently increase α-lipoprotein concentrations while androgens promptly lower them. The concentration of the lower density −S 25-40 β-lipoproteins either did not change or changed in a direction opposite to that of the α-lipoprotein. These workers attributed the partial immunity of women to coronary atherosclerosis either to the relatively large concentrations of α-lipoproteins or to the relatively high values for the high density/lower density lipoprotein ratio.

Lipoproteins have recently been measured in a variety of ways such as ultracentrifugation at various liquid densities, free electrophoresis, electrophoresis in starch blocks and in paper. This variation has made strict comparison of the different fractions impossible.

Paper electrophoresis has been used in study of sera from patients with myocardial infarction. Dangerfield and Smith[51, 52] noted an increase in what they called a "pre-β-lipid band" in the early stages. This band has

mobility slightly slower than α_2-globulin and would probably be comparable to the −S 20-25 and −S 40-70 (S_f 12-20) fractions. It is believed to be chemically distinct from the adjacent β-lipoproteins. Other low density lipoproteins trail behind the main β-lipoprotein peak while the chylomicrons do not migrate at all.

Besterman[53] found the pre-β band mainly in patients with atheroma but the association was not absolute. Well-defined bands were found in some healthy young men. Estrogen was the only substance found that reduced it. This study suggests that reduction in α-lipoprotein and increase in pre-β-lipoprotein is more pathognomonic than an increase in β-lipoprotein.

Since electrophoretic mobility is increased by injection of heparin into patients, it may be a source of confusion unless specifically noted in the treatment of patients with infarcts.

Some of the patients reported here were included in a cooperative study[4] of lipoproteins as predictors of myocardial infarction, in which we participated. During the subsequent follow-up period of up to 7 years after completion of this study of our subjects, additional infarctions occurred. The percentage of the people having high levels of cholesterol and S_f 12-20 and 20-100 lipoproteins at the initial study in this and in the cooperative study are similar.

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We wish to thank Dr. John Battle and Dr. William Proudfit of the Division of Medicine of the Cleveland Clinic for their generous cooperation.

Summary

Six normal women studied weekly for 5 months showed small variations in serum lipoproteins in the −S 40-70 fraction and much wider in the −S 1-10 and −S 70-400. In normal individuals the lipoprotein pattern is stable enough, if measured repeatedly, for comparison with patients. In 3 of the normal women the serum total cholesterol levels were stable and in the other 3 much less so. Single measurements of cholesterol or lipoproteins can be dangerously misleading.

The problem of levels of plasma proteins, cholesterol, and lipoproteins in their relationship to coronary atherogenesis, thrombosis, and myocardial infarction has remained unsettled. Most studies have been made after infarction and retrospective conclusions drawn. In our 7-year study during which 107 "normal" Cleveland executives were examined annually, 11 suffered infarction and 6 developed angina pectoris or coronary insufficiency, which provided data in the same individual before and after these events. When the changes occurring during the first 2 months after infarction are ignored, then little change in lipid levels is associated with these events.

Serum lipoprotein and electrophoretic protein patterns were studied in 84 patients shortly after myocardial infarction and in 66 repeatedly, at 5- to 10-day intervals for 3 to 4 weeks. Four of the patients were studied after a second infarction as well.

Most patients within a week of infarction showed increased β- and α_2-globulins with moderate increase in fibrinogen. Some exhibited increase in −S 20-25 and in low-density (−S 40-70 and 70-400) lipoproteins as well as the electrophoretic changes. Finally, a few had a progressive rise during the 2 to 3 weeks after infarction in low-density lipoproteins with a double peak appearing in the −S 25-40 component; α_2- and β-globulin increased greatly with some elevation of fibrinogen.

Serum cholesterol was higher in the young male patients with infarction, and lower in the oldest age group with infarction. Similar age trends did not occur in women.

After a second infarction, the low-density lipoproteins increased just as after the first one. A double peak appeared in the −S 25-40 fraction in half of these patients. The electrophoretic and lipoprotein changes after each infarction were strikingly similar.

There was little correlation between the lipoprotein pattern and severity of the in-

farction as measured by the electrocardiographic and clinical evidence. Increase in α_2-globulin was usually greatest in patients with the most extensive myocardial damage.

Three months to 10 years after infarction the range of lipoprotein values tended to fall within normal levels but continued to exhibit slight preponderance toward values higher than the mean "normal."

The "coronary profile" can be more sharply delineated by repeated measurement of serum cholesterol and lipoproteins. As a group, coronary atherosclerosis with myocardial infarction-prone people exhibit slightly elevated cholesterol and lipoprotein values.

Summario in Interlingua

Sex normal feminas studiate a intervallos septimanal durante 5 menses exhibiva nivellos seral de lipoproteinas que esseva micre in le fraction −S 40-70 e multo plus extense in le fractiones −S 1-10 e −S 70-400. Le condition del lipoproteinas in individuos normal, si mesurate repetitemente, es satis stabile pro permitter su uso in le comparation con observationes in patientes. In 3 del normal feminas in iste studio le nivellos del cholesterol total in le sero esseva stabile; in le 3 alteres, illos esseva multo minus stabile. Mesurationes individual de cholesterol o de lipoproteina pote esser fallacissime e riscose.

Le problema del relation inter (1) le nivellos de proteina, cholesterol, e lipoproteina in le plasma e (2) le occurrentia de atherogenese coronari, thrombose, e infarcimento myocardial remane sin responsa definitive. Le majoritate del studios del question esseva effectuate post le occurrentia de infarcimento, e le conclusiones derivate esseva de character retrospective. In nostre septenne studio, in le curso del qual 107 "normal" functionarios executive in le citate de Cleveland esseva examinate a intervallos annual, 11 suffreva infarcimento e 6 disveloppava angina de pectore o insufficientia coronari, de maniera que datos esseva obtenite ab le mesme individuo ante e post le mentionate eventos. Si le alterationes que occurre durante le prime 2 menses post le infarcimento es ignorate, le conclusion se impone que le nivellos lipidic es pauco alterate in association con ille eventos.

Lipoproteina seral e le comportamento electrophoretic de proteina esseva studiate in 84 patientes brevemente post le occurrentia de infarcimento myocardial. In 66, le studios esseva repetite a intervallos de inter 5 e 10 dies durante 3 a 4 septimanas. Quatro del patientes esseva etiam studiate post le occurentia de un secunde infarcimento.

In le majoritate del patientes, le determinationes effectuate durante le prime septimana post le infarcimento revelava augmentate valores pro globulina beta e alpha$_2$ e moderate augmentos del valores pro fibrinogeno. Plure patientes exhibiva augmentos in lipoproteinas −S 20-25 e in lipoproteinas de basse densitate (−S 40-70 e 70-400) si ben como le alterationes electrophoretic. Finalmente, plure patientes habeva un augmento progressive durante le periodo de 2 a 3 septimanas post le infarcimento in lor lipoproteinas a basse densitate, con le apparition de un duple culmine in le componente −S 25-40. Globulina alpha$_2$ e beta cresceva grandemente con un certe grado de elevation de fibrinogeno.

Le cholesterol del sero esseva plus elevate in juvene patientes mascule con infarcimento e plus basse in le gruppo del plus avantiate etates con infarcimento. Un simile tendentia non esseva observate in le patientes feminin.

Post le secunde infarcimento, le lipoproteinas de basse densitate se augmentava precisemente como post le prime infarcimento. In un medietate del patientes, un duple culmine appareva in le fraction −S 25-40. Le alterationes electrophoretic e lipoproteinic post le duo infarcimentos esseva frappantemente simile.

Esseva constatate pauc correlation inter le stato lipoproteinic e le severitate del infarcimento evalutate super le base de datos electrocardiographic e clinic. Le augmento de globulina alpha$_2$ esseva usualmente le plus pronunciate in le patientes con le plus extense affectiones myocardial.

A periodos de inter 3 menses e 10 annos post le infarcimento, le valores pro lipoproteina tendeva a restaurar se al area inter le extremos del valores de normal, sed illos continuava exhibir un leve preponderantia de nivellos superior al norma medie.

Le "profilo coronari" pote esser delineate plus nettemente super le base de repetite mesurationes del cholesterol e del lipoproteinas seral. Reguardate como un gruppo, subjectos con predisposition a atherosclerosis e infarcimento myocardial exhibi leve elevationes del valores pro cholesterol e lipoproteina.

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To Morgagni, not Rougnon, is due the credit of the first description of a single case. In the splendid section on aneurysm of the aorta, he describes angina pectoris accurately in Case V, referring to the paroxysms, the pain, the difficulty of breathing, the numbness of the left arm, and the effect of exertion. I read you here extracts from the case.

"A lady, forty-two years of age, who for a long time had been a valetudinarian, and within the same period, on using pretty quick exercise of body, she was subject to attacks of violent anguish in the upper part of the chest on the left side, accompanied with a difficulty of breathing and numbness of the left arm; but these paroxysms soon subsided, when she ceased from exertion. In these circumstances, but with cheerfulness of mind, she undertook a journey from Venice, purposing to travel along the continent, when she was seized with a paroxysm, and died on the spot. I examined the body on the following day. . . . The aorta was considerably dilated at its curvature; and, in places through its whole tract, the inner surface was unequal and ossified. These appearances were propagated into the arteria innominata. The aortic valves were indurated." He remarks: "The delay of blood in the aorta, in the heart, in the pulmonary vessels, and in the vena cava, would occasion the symptoms of which the woman complained during life; namely, the violent uneasiness, the difficulty of breathing, and the numbness of the arm. (Cooke's Morgagni).—WILLIAM OSLER, M.D. *Lectures on Angina Pectoris and Allied States*, 1897.

Relationship Between Plasma and Extracellular Fluid Volume Depletion and the Antihypertensive Effect of Chlorothiazide

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With the technical assistance of Mary J. Taylor

The importance of plasma and extracellular fluid volumes in the mechanism of the antihypertensive effect of chlorothiazide is disputed. The present investigation indicates that the lowering of blood pressure is accompanied by reductions in plasma and extracellular fluid volumes and in body weight. Furthermore, re-expansion of plasma volume with salt-free dextran reverses the antihypertensive effect. However, since gradual reaccumulation of extracellular fluid occurs during 1 year of continuous treatment, the *late* antihypertensive effects of chlorothiazide cannot be explained by the volume-depletion mechanism.

THE discovery of the antihypertensive action of chlorothiazide[1, 2] raised certain questions as to its mechanism of action. These questions included (1) whether the hypotensive response was caused by salt depletion or by some independent factor; (2) if produced by salt loss, by what mechanism it reduced blood pressure; (3) the factors that lead to increased reactivity to other antihypertensive agents; and (4) the reason for the moderate antihypertensive action of the drug when used alone in hypertensive patients and the absence of such activity in normotensive subjects.[3, 4] Complete answers to these questions cannot yet be given. This report concerns an attempt to elucidate some of the factors involved.

MATERIALS AND METHODS

Twenty male hypertensive patients with no symptoms or signs of congestive heart failure or edema were hospitalized and placed on a standard diet containing 1.5 Gm. of salt per day plus a supplement of 3 Gm. of salt in tablet form. This supplied a sodium intake of approximately 75 mEq. per day. Most of these patients were under treatment with other antihypertensive agents (table 1), which were continued during the entire period of study. A 4-day period for acclimatization to the diet was instituted in order to obtain stabilization of body weight and electrolyte excretions as well as average basal blood pressure readings. Determinations of plasma and extracellular volumes, serum electrolyte concentrations, and serum bicarbonate were carried out on the morning of the fifth day. Each patient was then given 500 mg. of chlorothiazide twice daily, and the studies were repeated after a period of 3 to 8 (average 6) days.

In 11 patients carefully screened for reliability and conscientiousness in regard to taking their medications, studies were repeated at approximately 6-month intervals for a period of 12 months. Seven of these patients were hospitalized and placed on the controlled salt intake for 2 to 3 days prior to repeating the determinations, while the remaining 4 were hospitalized for 1 day only because of their inability to take time out from work. Thus, dietary intake of salt cannot be regarded as well controlled in the long-term studies. At approximately 6 months following initiation of treatment the determinations of plasma and extracellular volumes in 7 patients were repeated. Chlorothiazide therapy was then discontiued for 1 week, after which another series of determinations were carried out. The patients remained hospitalized throughout this latter period.

Plasma volume was determined in the fasting subject after one half hour of rest in the supine position with the Evans blue dye method of Gibson and Evans[5] adapted and modified for use in the Coleman spectrophotometer,[6, 7] 3 specimens being

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TABLE 1.—*Data Following Short-Term Therapy with Chlorothiazide.*

Patient	Age	Other medication	Period of chlorothiazide treatment (days)	Blood pressure (mm. Hg)	Hematocrit (%)	Plasma volume (ml.)	Thiocyanate space (L.)	Body weight (Kg.)	Serum concentrations (mEq./L.) Na	Cl	K	CO_2
C.E.	46	—	8	—20/15	+2.1	—412	— .9	—2.0	—5	+5	—.3	
J.Wr.	47	Reserpine	6	—26/16	+4.4	—501	— .9	— .9	—4	—7	+.1	
N.M.	60	Reserpine	6	—17/6	+5.0	—783	—2.4	—3.3	—3	0	—.6	
A.J.	46	Reserpine	7	—36/14	+ .5	—132	— .3	+1.3	+5	—10	—.8	
J.Br.	43	Reserpine	7	—30/20	+3.0	—319	+ .1	+2.0	—1	0	—.3	
J.Bu.	60	Reserpine	7	—15/10	+2.2	—568	—1.9	—2.7	+4	0	+.1	0
H.K.	40	Reserpine	8	—20/20	+1.7	— 66	— .5	—1.2	—5	0	—.4	—1
J.Z.	57	Reserpine	5	—10/0	+1.0	—296	—3.9	—2.2	+3	—10	—.5	
A.N.	64	Reserpine	5	—20/5	— .4	— 55	—1.4	— .7	+1	+1	—.7	
N.B.	50	Reserpine	7	—15/15	+1.8	—460	—3.6	—4.0	—3	—2	—.2	
J.We	66	Reserpine and Hydralazine	6	—40/18	+4.2	—265	—5.8	—4.6	0	—4	—.2	
C.S.	36	Reserpine and Hydralazine	6	—14/20	+3.0	—741	—4.0	—1.4	—4	+9	—.2	
T.H.	66	Reserpine and Mecamylamine	6	—40/25	+1.4	—598	—2.4	—3.0	—2	0	—.3	
J.C.	47	Reserpine and Mecamylamine	4	—20/22	+ .5	—363	— .5	+ .2	—4	0	+.2	—1.4
C.P.	52	Reserpine and Mecamylamine	8	—50/30	+1.1	—177	—2.1	—2.2	—2	0	—.3	—1
M.P.	46	Reserpine and Mecamylamine	8	—25/10	+4.4	—222	1.1	—1.0	—3	+6	—.3	
G.B.	44	Reserpine and Chlorisondamine	8	—30/10	+4.2	—403	—2.0	—1.5	—3	—6	—.7	
J.D.	47	Reserpine and Chlorisondamine	6	—10/10	+1.4	— 39	—3.8	— .2	—1	—.1	—.2	
M.C.	42	Reserpine and Chlorisondamine	3	—10/25	+ .4	—172	+ .4	—2.3	—1	—4	—.2	
S.E.	42	Reserpine, Hydralazine, Pentolinium	7	—25/15	+2.0	—596	—4.6	—5.4	+2	0	—.6	+1
Mean			6.4	—24/—15*	+2.2*	—358*	—2.1*	—1.8*	—1.3	—1.1	—.32*	—.5
S. D.				11/7.5	4.9	223	1.75	1.84	2.9	4.8	2.74	1.8

*p value less than .001.

used at 10, 15, and 20 minutes for determining dye dilution. The hematocrit value was determined from the average of 6 samples drawn during the various experimental procedures. Eighteen milliliters of 5 per cent sodium thiocyanate* were injected usually at the end of the plasma volume determinations and samples were drawn at 2 and 3 hours for determination of thiocyanate space according to the method of Crandall and Anderson[8] adapted to the Coleman spectrophotometer. Radiosulfate space was determined with S^{35}-labeled sulfate by the method of Walser.[9] Sodium and potassium were determined with a flame photometer. Serum chloride was determined by the method of Schales and Schales[10] and serum bicarbonate by a modification of the method of Van Slyke.[11]

All injectates were given in calibrated syringes; blood samples were drawn with minimal stasis. Blood pressure was determined by the auscultatory method before and after each experimental period. The patients were weighed prior to the procedures on a beam balance accurate to ± 250 Gm.

The cumulative negative balances of sodium, potassium, and chloride during the first 3 to 4 days of chlorothiazide treatment were estimated as follows: beginning 48 hours after institution of the diet 3 consecutive 24-hour collections of urine

*Kindly supplied by Eli Lilly and Company, Indianapolis, Ind.

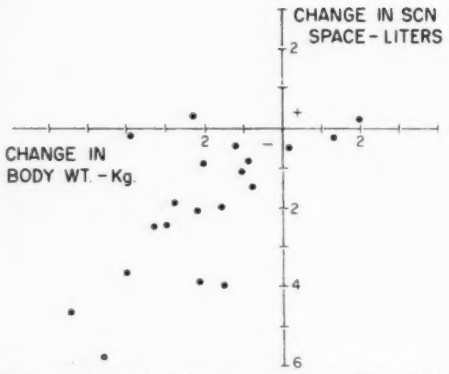

FIG. 1. Relationship between change in body weight and in thiocyanate space following short-term treatment with chlorothiazide.

were analyzed for total sodium, chloride, and potassium, and the average was taken as the control level of excretion. The cumulative elevations above this level during the first 3 to 4 days after chlorothiazide were then used to estimate electrolyte losses.

The effect of restoration of the plasma volume was determined in 7 patients who exhibited significant hypotensive responses to chlorothiazide. Each patient received 500 ml. of 6 per cent dextran in normal saline; and after several days the procedure was repeated with substitution of a similar volume of dextran in 5 per cent glucose in water. The infusion rate was approximately 25 ml. per minute. Blood pressure and heart rate were determined repeatedly before and throughout the procedure and blood for hematocrit determinations was drawn immediately preceding and following each infusion.

RESULTS

Acute Effects of Chlorothiazide

Following 3 to 8 (mean 6) days of chlorothiazide therapy the plasma volume showed some reduction in all of 20 nonedematous hypertensive patients (table 1). The loss of plasma volume averaged 358 ± 223 ml. and varied in different patients from insignificant falls of less than 70 ml. to rather marked losses above 700 ml. The hematocrit reflected the plasma volume change in an approximate way by exhibiting slight to moderate elevation. However, there was no close quantitative relationship between hematocrit and plasma volume changes.

TABLE 2.—*Losses after Chlorothiazide*

Patient	Chlorothiazide treatment (days)	Urinary losses, cumulative negative balance (mEq.) Na	Cl	K	Change after chlorothiazide: Thiocyanate space (L.)	Wt. (Kg.)
S. E.	3	224	392	209	—4.6	—5.4
J. Bu.	4	301	489	181	—1.9	—2.7
N. M.	4	290	560	168	—2.4	—3.3
J. Z.	3	162	135	154	—3.9	—2.2
J. T.	4	216	268	4	— .7	—2.2
E. W.	3	349	510	222	—3.4	—2.7
Average	3.5	257*	392*	156.3*	2.8*	3.0*
S. D.		68	163	71	1.4	1.2

*p value less than .005.

The thiocyanate space declined by more than 0.5 L. in all except 5 of the 20 cases (table 1). For the group as a whole the mean reduction was 2.1 ± 1.75 L. Although the reductions of both plasma and available fluid spaces were significant ($p < .001$), there was no consistent relationship between the degree of plasma volume and available fluid changes.

Body weight decreased in 16 of the 20 patients (mean 1.8 ± 1.84 Kg.). The change in body weight was significant at the .001 level. There appeared to be a rough correlation between the extent of change in body weight and in thiocyanate space (fig. 1). The blood pressure fell in all patients, the average change being –24/15 mm. Hg. The reduction occurred during the first 48 hours following institution of chlorothiazide. There was no quantitative correlation between the plasma volume and arterial pressure changes.

The cumulative losses of body electrolytes (cumulative negative balance) by the end of the third to fourth day of chlorothiazide treatment averaged 257 ± 68 mEq. of sodium, 392 ± 163 mEq. of chloride, and 156 ± 71 mEq. of potassium in 6 patients studied (table 2). All of these patients exhibited significant reductions in body weight and thiocyanate space. The correlation between the extent of body weight reduction and electrolyte losses was poor in this small series. However, the accuracy of 24-hour urine collections cannot

TABLE 3.—*Effects of Intravenous Infusion of Six Per Cent Dextran in Saline and of Salt-free Dextran*

Patient	Chlorothiazide treatment (mos.)	Control B.P. (mm.Hg)	After chlorothiazide change	Following dextran infusion			
				In 5 per cent glucose change		In normal saline change	
			mean B.P.* (%)	Mean B.P. (%)	Hematocrit (%)	Mean B.P. (%)	Hematocrit (%)
J.H.†	1.0	150/110	—16.2	+10.0	— 3.2	+ 9.0	— 5.8
J.C.†	.5	180/110	—22.9	+18.4	—11.4	+20.0	—12.0
C.S.‡	3.0	150/110	—13.0	+10.5	—12.1	+10.0	—12.8
R.C.‡	1.0	180/108	—30.4	+28.1	— 9.1	+23.7	—12.6
W.F.†	1.0	140/100	—11.3	+14.0	—13.6	+13.2	— 9.8
N.B.‡	1.0	145/95	—12.5	+19.0	— 8.8	+17.0	— 6.0
J.Z.†	2.0	142/96	—10.9	+ 8.4	— 5.0	—	—
Mean	1.4	155/104	—16.7§	+15.4§	— 9.0♯	+15.4♯	— 9.8♯
S.D.			8.8	6.9	3.8	5.8	3.3

*"Mean" blood pressure equals (systolic + diastolic)/2.

†On no other antihypertensive drugs.

‡Also receiving reserpine 0.25 mg. per day. C.S. also taking hydralazine 25 mg. t.i.d.

§p value less than .005.

♯p value less than .001.

be regarded as completely reliable, even in hospitalized patients. The changes in the serum concentrations of sodium and chloride were insignificant, but there was a small but significant decrease in potassium (table 1). The serum bicarbonate determined in 4 patients showed essentially no change.

Acute Restoration of Plasma Volume

The effect of re-expansion of plasma volume on blood pressure was determined in 7 patients who had been under continuous treatment with chlorothiazide for periods ranging from 2 weeks to 3 months (mean 1.4 months). These patients had exhibited reductions of "mean" (systolic + diastolic)/2 blood pressure averaging 17.0 ± 9.0 mm. Hg (table 3). The administration of 6 per cent dextran in isotonic saline in 6 of these patients resulted in an immediate elevation of blood pressure averaging 15.0 ± 6.0 mm. Hg. The mean percentage fall in the hematocrit was 9.8 ± 3.3 during the dextran infusion.

In order to determine whether sodium ion was important in the reversal of the antihypertensive effect the infusions were repeated after several days with 6 per cent dextran in 5 per cent glucose in water. In 7 patients a significant elevation of blood pressure was observed ranging between 8 to 28 mm. Hg (mean + 15.0 ± 7.0 mm. Hg, ($p < .005$) The percentage fall of hematocrit averaged 9.0 ± 3.8.

Effects of Long-Term Treatment with Chlorothiazide

Whereas the reductions in plasma volume, thiocyanate space, and body weight were significant during short-term therapy with chlorothiazide, this was not the case following long-term treatment. In 11 patients when these parameters were measured at the end of 6 months, only the reduction in thiocyanate space remained significant (table 4). At the end of 1 year the change in thiocyanate space was no longer significant at the .05 level. Despite this trend, however, the blood pressure changes, although not as marked at the end of 1 year as in the early stages of therapy, still showed significant reductions.

In 9 patients after 1 to 3 months (average 1.8 months) the extracellular fluid volume was estimated by means of 2 indicators (table 5), thiocyanate and radiosulfate simultane-

TABLE 4.—*Changes Initially after Six and Twelve Months*

	Plasma volume (ml.)			Blood pressure (mm. Hg)			Thiocyanate space (L.)			Body weight (Kg.)		
Patient	1 wk.	6 mo.	12 mo.	1 wk.	6 mo.	12 mo.	1 wk.	6 mo.	12 mo.	1 wk.	6 mo.	12 mo.
J.We.	—265	— 22	+165	—40/—18	—30/—15	0/—8	—5.8	—3.9	— .7	—4.6	—1.1	—2.8
J.Wr.	—501	— 42	—212	—26/—16	—22/—20	— 7/0	— .9	—2.2	— .2	— .9	—6.0	—6.1
C.S.	—741	—201	—225	—14/—20	—20/—20	—30/—30	—4.0	—3.2	—1.2	—1.4	—8.0	—4.9
N.M.	—783	+ 74	+132	—17/—6	—20/—19	—35/—14	—2.4	—2.4	+1.2	—3.3	+ .2	—1.0
T.H.	—598	+110	—168	—40/—25	—30/—20	—20/—10	—2.4	— .4	— .7	—3.0	+7.7	+6.7
S.E.	—596	+ 58	— 19	—25/—15	—20/—20	—20/—22	—4.6	—4.7	+ .9	—5.4	—6.3	+5.7
J.C.	—363	—323	—402	—20/—22	—30/—20	30/—5	— .5	— .5	— .1	+ .2	+ .9	+4.9
J.Br.	—319	—248	—534	—30/—20	—28/—15	—10/0	+ .1	—2.1	—2.1	+2.0	+4.4	+1.9
J.Bu.	—568	—164	—336	—15/—10	—15/—20	—10/—15	—1.9	— .8	— .6	—2.7	+ .8	—1.4
C.P.	—177	— 51	— 51	—50/—30	—30/—20	—18/—20	—2.1	—1.1	—1.5	—2.2	—4.3	—7.0
H.K.	— 66	— 75	— 56	—20/—20	—20/—20	—20/—15	— .5	— .9	— .7	—1.2	— .1	+ .1
Mean	—452*	— 80	—155†	—27/18*	—24/19*	—18/13*	—2.3‡	—2.0‡	— .6	2.0‡	—1.0	— .4
S. D.	232	128	212	11.6/6.8	5.5/2	10.5/2.4	1.8	1.5	.9	2.1	4.6	4.7

*p value less than .001.
†p value less than .05.
‡p value less than .01.

TABLE 5.—*Comparative Changes in Extracellular Fluid Volume before and after Chlorothiazide As Measured by Two Different Indicators*

	Duration treatment	Thiocyanate space (L.)			S^{35}-labeled sulfate space (L.)			Thiocyanate change	S^{35} change
Patient	(mos.)	Control	After drug	Change	Control	After drug	Change	(%)	(%)
J.W.	2	25.4	23.2	—2.2	19.9	15.7	—4.2	—11.5	—21
N.M.	3	19.8	17.4	—2.4	14.1	13.6	—0.5	—12	—4
A.J.	2	24.0	21.7	—2.3	17.7	17.3	— .4	—10	—2
T.H.	1	25.6	25.0	— .6	19.6	19.6	—0	—2	0
S.E.	1	24.5	21.1	—3.4	18.3	16.0	—2.3	—14	—13
J.Bu.	2.5	19.0	18.2	—1.8	14.4	13.2	—1.2	—11	—12
J.Br.	1	22.4	18.9	—3.5	18.6	15.8	—2.8	—16	—15
C.P.	1	18.9	16.3	—2.6	15.8	14.1	—1.7	—14	—11
H.K.	1	17.1	16.8	— .3	13.2	12.4	— .8	—2	—6
Mean	1.83	21.8	19.9	—2.1*	16.8	15.3	—1.5	—10.3*	—9.3†
S.D.				1.1			1.3	5	7.3

*p value less than .001.
†p value less than .05.

ously, as an additional check on the validity of the change demonstrated with thiocyanate alone. Considerably more variation was observed with radiosulfate as the indicator. However, the average change for the group as a whole was similar with either thiocyanate or S^{35}-labeled sulfate and the reduction in estimated extracellular space was still significant with either method.

Chlorothiazide was withdrawn for a 1-week period in 8 patients after 3 to 7 (average 5.4) months of contiuous treatment in order to evaluate the changes that might occur following discontinuation of long-term therapy (table 6). There was a prompt elevation of plasma volume averaging 241 ± 100 ml., a rise in blood pressure (mean 23/15 ± 8/9 mm. Hg), and a gain in body weight averaging 1.6 ± 1.3 Kg. All these changes were significant at the .01 level or less. The in-

TABLE 6.—*Changes Following Discontinuation of Chlorothiazide*

'atient	Duration treatment (mos.)	Plasma volume (ml.)			Blood pressure (mm. Hg)			Thiocyanate space (L.)			Body weight (Kg.)		
		After chlor.	Repeat control	Gain or loss	After chlor.	Repeat control	Gain or loss	After chlor.	Repeat control	Gain or loss	After chlor.	Repeat control	Gain or loss
'.We.	4	3720	3827	+107	170/100	200/120	+30/20	23.	26.9	+2.1	85.3	85.3	0
'.Wr.	7	3717	4106	+389	151/103	180/130	+29/27	26.4	25.4	—1.0	103.3	104	+ .7
'.S.	7	3537	3871	+234	128/87	150/110	+22/23	19.6	20.7	+1.1	73.0	74.3	+1.3
T.H.	7	3943	4152	+209	153/100	160/110	+ 7/10	24.7	25.6	+ .9	92	94.3	+2.3
S.E.	7	3183	3525	+342	160/110	180/125	+20/15	24.2	25.6	+1.4	71.5	72.7	+1.2
J.C.	5	3340	3663	+323	170/100	200/110	+30/10	22.8	23.0	+ .2	95.4	99.5	+4.1
J.Br.	3	3200	3350	+150	140/100	165/100	+25/0	18.9	22.4	+3.5	80.3	83.0	+2.7
H.K.	3	2931	3106	+175	130/90	150/110	+20/20	16.4	17.2	+ .8	70	70.7	+ .7
Average	5.4	3446	3700	+241*	150/99	173/144	+23*/15†	21.5	23.4	+1.1	83.8	85.2	+1.6†
S.D.				100.4			7.8/8.8			1.4			1.3

*p value less than .001.

†p value less than .05.

crease in thiocyanate space averaged 1.1 ± 1.4 L. The latter change was of questionable significance ($p < .06$).

As compared to pretreatment values it was of interest that following discontinuation of the drug plasma volume increased 120 ± 18 ml. and thiocyanate space rose to 0.5 ± 0.3 L. above the original, untreated level. These slight overshoots were not accompanied by parallel behavior of the blood pressure, the latter remaining –4/6 ± 7/7 mm. Hg below the pretreatment level.

The changes in serum electrolyte concentrations and in serum bicarbonate were determined after 1 year of chlorothiazide treatment in 11 patients (table 7). Serum sodium concentrations were essentially unchanged. Serum chloride levels decreased slightly in most patients but increased slightly in 2, the average change being 4.4 ± 6.8 mEq. There was a significant decline in serum potassium concentrations. The mean reduction was 1.1 ± 0.6 mEq. (p .001). The serum bicarbonate remained unchanged.

DISCUSSION

In the present observations the reduction of blood pressure paralleled the saluresis and did not precede or follow it. The saluretic effect was essentially complete in 48 hours. The question arises as to the source of the sodium depletion, specifically as to whether it represented reductions in intracellular stores or came from the extracellular fluid. The maintenance of normal serum sodium levels indicated that the drug did not extract sodium from the extracellular water. However, the extent of the depletion of extracellular fluid volume indicated that the majority if not all of the sodium removed could be accounted for by an excretion of isotonic, extracellular fluid. This is in keeping with the observations on other saluretic agents such as mercurials, which produce primarily a reduction of extracellular fluid volume.[12]

Since the plasma volume is in equilibrium with the interstitial fluids, it also shared in the general reduction of extracellular fluid space. However, the relationship between change in extracellular and plasma volumes is only approximate.[13] Because of the failure to find any evidence for significant cellular losses of sodium, the question arose whether the antihypertensive effect was related simply to the decrease in total circulating blood volume and to a reduction in tissue pressure secondary to the extracellular fluid loss. Such an interpretation is supported by the observation of Crosley and his associates[14] that right heart pressures and cardiac output are reduced by chlorothiazide. Preliminary

TABLE 7.—*Changes Following One Year of Treatment with Chlorothiazide*

Patient	Change in mEq.			
	Na	Cl	K	CO_2
J.We.	—3	— 4	— .8	—1.
J.Wr.	—1	—12	— .3	—1.6
C.S.	0	— 9	— .6	—2.0
N.M.	—1	— 9	— .6	+4.8
T.H.	+2	—11	—1.1	+3.1
S.E.	0	— 8	—1.5	+3.2
J.C.	—4	— 1	— .4	+2.0
J.Bu.	—5	+ 9	—1.2	—3.0
J.Br.	—1	— 3	— .4	—1.0
C.P.	—4	+ 5	—2.1	—4.0
H.K.	0	— 5	—1.0	+1.0
Mean	—1.5	— 4.4*	— .95†	+ .2
S.D.	2.5	6.8	.6	2.9

*p value less than .05.
†p value less than .001.

results in this laboratory tend to confirm these observations. Dustan and her co-workers[15] also found a reduction in cardiac output following chlorothiazide.

If the antihypertensive effects of chlorothiazide were due to a change in intracellular sodium concentration producing a decrease either in arteriolar tone or a dehydration of "waterlogged" arterioles,[16] the hemodynamic effects should be reflected in a reduction of total peripheral resistance rather than a fall in cardiac filling pressures and output. The latter findings, however, are readily explained by the decreases in plasma and extracellular fluid volumes. It is of interest that the normotensive individual compensates so that the basal blood pressure is not lowered, whereas this compensation seems to be deficient in hypertensive patients.[3, 4] Whether such failure of homeostasis is due to a decreased responsiveness of the baroreceptors or to other factors cannot be determined on the basis of present evidence.

The importance of the plasma volume change in the mechanism of the antihypertensive effect was indicated by the fact that restoration of plasma volume either with or without any replenishment of sodium restored the blood pressure to essentially pretreatment levels. The lack of a quantitative relationship between the decrease in plasma volume and the fall of blood pressure can be explained on the basis of variations in the activity of compensatory mechanisms including the baroreceptor reflexes, and intrinsic vascular distensibility in different individuals. This variability was further enhanced by the fact that some of the patients were taking ganglion-blocking drugs and others were not.

These conclusions on the importance of oligemia in the mechanism of the antihypertensive action of chlorothiazide confirm our initial findings[3] and are similar to those expressed by Dustan, Tapia, and associates.[15, 17] They propose that the oligemia enhances vasomotor "tone" which in turn makes the patient more responsive to ganglion-blocking agents. However, the observation that the hypertensive patient often shows some reduction of blood pressure with chlorothiazide alone whereas the normotensive subject does not[3, 4] suggests that the compensatory mechanisms for plasma volume depletion often are inadequate in hypertension. Also, the decreased responsiveness to norepinephrine following chlorothiazide[18, 19] in normotensive subjects is not readily explained on the basis of increased vasomotor tone alone, and suggests that reactivity is dependent to some extent on the degree of filling of the vascular system.

The failure to observe a significant reduction of plasma volume after 6 to 12 months of treatment reflects either tolerance to the saluretic effects of the drug or the establishment of compensatory mechanisms for restoration of homeostasis. Compensatory mechanisms become active after the first 48 hours of treatment when the output of sodium comes back into balance with the intake. However, in the first month of treatment the depletion achieved during the initial saluresis is maintained and only gradually, thereafter, is the plasma volume deficit made up.

Other investigators have postulated that chlorothiazide may have antihypertensive effects additional to its saluretic action.[4] This

s based on the observation that the blood pressure remains below pretreatment levels after the body weight has been restored. It should be pointed out, however, that disappearance of acute drug effects without return to pretreatment levels of blood pressure is not unique for chlorothiazide. For example, the acute hemodynamic effects of hydralazine, characterized by tachycardia and palpitation reflecting an increase in cardiac output, generally disappear with long-term treatment. Similarly, the manifestations of ganglionic blockade such as impaired visual accommodation, dry mouth, and postural hypotension often diminish with long-continued therapy even though basal arterial pressure remains below the pretreatment level. The observations of Perry and Schroeder[20] indicate that vigorous treatment to obtain a continuous and prolonged reduction of arterial pressure, often modifies the severity of the hypertension, so that less intensive or no further treatment is required. Thus, after long-term therapy many factors, such as tolerance, compensatory reactions, and modification of the basal level of blood pressure, come into play to obscure the initial relationship between drug action and antihypertensive effect. It does not seem possible to draw valid conclusions concerning the antihypertensive activity of a drug at this late stage, especially if the effects of drug withdrawal are not determined.

Summary and Conclusions

Plasma and extracellular fluid volumes, serum electrolyte concentrations, arterial pressure, body weight, and electrolyte excretions were determined in hypertensive patients treated with chlorothiazide.

Plasma and extracellular fluid volumes decreased promptly during the early phases of treatment. This was accompanied by a reduction of arterial pressure and body weight. Sodium losses could be accounted for on the basis of extracellular fluid volume depletion. Restoration of plasma volume either with or without partial replenishment of sodium reversed the antihypertensive effect of chlorothiazide. Withdrawal of chlorothiazide after 3 to 7 months of treatment was followed by an elevation of plasma volume usually to levels slightly above the control. Blood pressure rose to levels slightly below the control.

Significant reductions of plasma volume and body weight were not found after 6 months and of extracellular fluid volume after 12 months of therapy even though the blood pressure remained reduced. However, the latter may not be a valid criterion of drug activity following long-term modification of the blood pressure level. The only significant change in serum electrolyte concentration was a reduction in serum potassium. Serum bicarbonate levels were not altered.

On the basis of this and other evidence discussed it is suggested that the decrease in plasma volume is an important factor producing the initial antihypertensive effect. Reduction in tissue pressure secondary to extracellular fluid volume depletion also could contribute to this response.

Summario in Interlingua

Le volumines del plasma e del liquido extracellular, le concentrationes del electrolytos in le sero, le tension arterial, le peso corporee, e le excretion de electrolytos esseva determinate in patientes hypertensive subtractamento con chlorothiazido.

Le volumines de plasma e de liquido extracellular descendeva promptemente durante le phases initial del tractamento. Isto esseva accompaniate per un reduction del tension arterial e del peso corporee. Le perditas de natrium esseva explicabile super le base del depletion del volumine de liquido extracellular. Le restauration del plasma, tanto con como etiam sin le restitution partial de natrium reverteva le effecto antihypertensive de chlorothiazide. Le privation de chlorothiazido post 3 a 7 menses de tractamento esseva sequite per un elevation del volumine del plasma, usualmente usque a nivellos levemente supra le nivellos de controlo. Le tension del sanguine montava usque a nivellos levemente infra le nivellos de controlo.

Significative reductiones del volumine del plasma e del peso corporee non esseva constatate post 6 menses de therapia, e similemente nulle significative reductiones del volumine del liquido extracellular esseva constatate post 12 menses de therapia ben que le tension de sanguine remaneva reducite. Tamen, iste ultime facto es possibilemente invalide come criterio del activitate del droga post un prolongate modification del nivello del tension de sanguine. Le sol significative alteration in le concentration de electrolytos in le sero esseva un reduction del contento de kalium. Le nivellos de bicarbonato in le sero non esseva alterate.

Super le base de iste e altere observationes discutite in le presente reporto, le these es formulate que le reduction del volumine del plasma es un importante factor in le production del effecto antihypertensive initial. Le reduction del pression del histos que seque le depletion del volumine de liquido extracellular es etiam possibilemente un contributor a ille responsa.

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Evaluation of Chlorothiazide Alone in the Treatment of Moderately Severe and Severe Hypertension

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The effectiveness of alternate 6-month courses of chlorothiazide alone with standard antihypertensive therapy is compared in 11 patients with severe hypertension and 30 patients with moderately severe hypertension. These results are then compared with those of a 6-month combined treatment period when the patients received both chlorothiazide and standard antihypertensive therapy.

ALTHOUGH studies in many clinics have demonstrated the potentiation of antihypertensive agents by chlorothiazide,[1-3] its value alone in patients with moderately severe and severe hypertension has not been established. This investigation was designed to compare the effectiveness of alternate 6-month courses of chlorothiazide alone with standard antihypertensive therapy, and to compare the results of these periods with those of a 6-month combined treatment period when patients received both chlorothiazide plus standard antihypertensive therapy.

METHODS AND MATERIALS

Forty-one patients were chosen from the Hypertensive Clinic of the District of Columbia General Hospital, 11 with severe hypertension and 30 with moderately severe hypertension. The pertinent data are presented in tables 1 and 2.

Experimental Plan. Each patient was followed through 4 study periods. A 1-month no treatment period, a 6-month chlorothiazide period, a 6-month standard therapy period, and a 6-month combined therapy period. The only indication for not strictly adhering to this experimental plan was the presence of fulminating disease in some of the patients with severe hypertension that necessitated the addition of further therapy. In order to avoid the influence of climate, one half the patients of each group were started on the chlorothiazide period during the summer months and the other half during the winter months.

During the "no treatment period" and during the first 2 months of each of the other treatment periods the patients visited the clinic weekly. During the remainder of the study clinic visits were biweekly. At the beginning of the study all the patients underwent the routine clinical and laboratory studies, including a complete history and physical examination, urinalysis, blood urea nitrogen determination, electrocardiogram, and chest roentgenogram. These laboratory procedures were repeated during each study period.

The dose of chlorothiazide (Diuril) was 1 Gm. a day (500 mg. twice a day) in all patients. The patients were allowed to eat a regular diet; supplemental potassium was not administered. During the period of standard therapy the patients with severe hypertension received mecamylamine (Inversine) and reserpine (Harmonyl). The daily dose of reserpine was 0.25 mg. The dose of mecamylamine was individualized and ranged between 15 and 36 mg. per day. During the period of standard therapy the patients with moderately severe hypertension received veratrum (Veriloid) and reserpine (15 patients) or hydralazine (Apresoline) plus reserpine (15 patients). The dose of reserpine was 0.25 mg. The dose of veratrum ranged between 9 and 16 mg. per day and the dose of hydralazine ranged between 200 and 300 mg. per day.

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TABLE 1.—*Severe Hypertensive Group*
(11 patients, 8 ♀ and 3 ♂)

Average	Age—45 years (34-66) Duration of hypertension—6 years (7 mos.-16 yrs.) Mean arterial pressure—170 ± 26.4 mm. Hg BUN—24 mg. per cent (9-35)
Fundi	Grade III (8 pts.) Grade IV (3 pts.)
X-ray	Large heart (10 pts.) Minimal cong. failure (3 pts.—controlled by digitalis)
ECG	Left ventricular hypertrophy (9 pts.)

TABLE 2.—*Moderate Hypertensive Group*
(30 patients, 24 ♀ and 6 ♂)

Average	Age—48 years (36-62) M.A.P.—160 ± 21.6 mm. Hg BUN—14 mg. per cent (9-26)
Fundi	Grade II (all patients)
X-ray	Enlarged heart (16 pts.) Minimal cong. failure (3 pts.—controlled by digitalis)
ECG	Normal—11 pts. Old infarction—2 pts. Bundle-branch block—3 pts. L V H—14 pts.

Soon after the beginning of the combined treatment period it was necessary to reduce the dose of mecamylamine in the patients with severe hypertension by one third to one half in order to avoid severe postural hypotension. If the level of arterial pressure did not increase following such a reduction in dosage an attempt was then made to substitute veratrum or hydralazine for the ganglionic-blocking agents. Similarly, in the patients with moderately severe hypertension chlorothiazide necessitated a reduction of dosage of both veratrum and hydralazine. If the level of arterial pressure did not increase in these patients, an attempt was made to discontinue hydralazine and veratrum.

RESULTS

Severe Group

Standard Therapy vs. Chlorothiazide Therapy. The results of the first part of this study are shown in table 3. A 9-per cent reduction in mean arterial pressure (MAP) resulted from both chlorothiazide and mecamylamine plus reserpine in 5 patients. In an additional 3 patients a 10-mm. reduction in mean arterial pressure occurred under chlorothiazide therapy. Despite the moderate reduction in mean arterial pressure in both groups there was no significant change in the severity of the vascular disease, e.g., fundi, heart, kidneys. A rising arterial pressure and the development of fresh retinal hemorrhages necessitated the addition of chlorothiazide to ganglionic-blocking therapy at the end of 2 months in 3 patients.

Combination Therapy. The data resulting from the addition of chlorothiazide to standard therapy are outlined in table 4. During the first 2 months of this period the dose of mecamylamine could be reduced by one half in all but 2 patients. Such combination therapy resulted in a 16-per cent reduction in mean arterial pressure below the no treatment level and a 7-per cent reduction below the lowest previous level. More important, however, was the reversal of papilledema in 3 patients, clearing of hemorrhages and exudates in 5 patients, and a decrease in heart size in 5 patients.

At the end of the fourth month of this period hydralazine in a daily dose of 300 mg. and veratrum in a daily dose of 9 mg. could be substituted for mecamylamine in 7 and 3 patients respectively. The excellent therapeutic results continue in these patients at the present time (5 months follow-up). Continued use of mecamylamine was necessary in 1 patient.

Moderately Severe Group

Standard Therapy vs. Chlorothiazide Therapy. The data from the chlorothiazide period are compared with those from the standard treatment period in table 5 where it can be noted that a comparable reduction in average arterial pressure occurred in both groups. Further analysis of these data shows that more than a 20-mm. reduction in mean arterial pressure followed both chlorothiazide alone and standard therapy in 13 patients, followed standard therapy alone in 4 patients, and followed chlorothiazide therapy alone in 2 patients. Expressed in a different way, it can be stated that standard therapy was successful in 17 patients (13 plus 4)

TABLE 3.—*Severe Hypertensive Group—11 Patients*

ose	No treatment—1 mo.	Chlorothiazide—6 mos. (1 Gm./day)	Mecamylamine + Reserpine—6 mos. (15-36 mg./day + 0.25 mg./day)
lean arterial pressure	170 ± 26.4 mm. Hg	153 ± 17.3 mm. Hg (9%↓)	155 ± 19.3 mm. Hg (9%↓)
undi	Grade III—8 pts. Grade IV—3 pts.	No change	No change
-ray	Enlarged heart—10 pts.	Further enlargement of heart—1 pt.	Further enlargement of heart—2 pts.
ong. failure	Minimal—3 pts.	Less—2 pts.	No change
CG	L V H—9 pts.	Less—L V H—3 pts.	No change
UN	24 mg. per cent (9-35)	No change	No change

TABLE 4.—*Severe Hypertensive Group—11 Patients*

Dose	Chlorothiazide—6 mos. (1 Gm./day)	Mecamylamine + Reserpine—6 mos. (15-36 mg./day + 0.25 mg./day)	Mecamylamine* + Reserpine + Chlorothiazide—6 mos. (5-15 mg./day + 0.25 mg./day + 1 gm./day)
Mean arterial pressure	153 ± 17.3 mm. Hg (9%↓)	15.5 ± 19.3 mm. Hg (9%↓)	143 ± 17.6 mm. Hg (16%↓)
Fundi	No change	No change	Grade IV→II—3 pts. Grade III→II—5 pts.
X-ray	Further enlargement of heart—1 pt.	Further enlargement of heart—2 pts.	Decrease in heart size—5 pts.
Cong. failure	Less—2 pts.	No change	Only satisfactory therapy—3 pts.

*By fourth month 300 mg. hydralazine or 9 mg. veratrum could be substituted for mecamylamine in 10 of 11 patients.

and chlorothiazide was successful in 15 patients (13 plus 2) or 50 per cent of the patients with moderately severe hypertension.

Combined Treatment Period. The data resulting from the addition of chlorothiazide to standard treatment in the 30 patients with moderately severe hypertension are presented in table 6. The addition of chlorothiazide to either veratrum or hydralazine resulted in a 17-per cent reduction in mean arterial pressure as compared to the no treatment level and an 8-per cent reduction in mean arterial pressure below the lowest previous treatment level. In each patient the addition of chlorothiazide resulted in more than a 10-mm. reduction in mean arterial pressure below the lowest previous level. Such combination therapy also resulted in complete clearance of congestive heart failure present in 3 patients. The addition of chlorothiazide permitted reduction in the dosage of hydralazine in 12 of 15 patients and a reduction in dosage of veratrum in 13 of 15 patients. During the last 2 months of the combined treatment period it was possible to discontinue hydralazine in 10 patients and veratrum in 13 patients, chlorothiazide plus reserpine serving as the sole antihypertensive agents. The excellent therapeutic results continue in these patients at the present time (5 months follow-up).

DISCUSSION

Neither chlorothiazide alone nor ganglionic-blocking agents plus reserpine represented effective treatment in the patients with severe

TABLE 5.—*Moderate Hypertensive Group—30 Patients*

	Chlorothiazide—6 mos.	Veratrum—15 pts. + Reserpine (6 mos.) or Hydralazine—15 pts.	Veratrum*—15 pts. or Hydralazine* (15 pts.) + Reserpine + Chlorothiazide —6 mos.
Dose	1 Gm./day	Veratrum—9-16 mg./day Hydralazine—200-300 mg./day Reserpine—0.25 mg./day	Veratrum—6-9 mg./day Hydralazine—100-200 mg./day Reserpine—0.25 mg./day Chlorothiazide—1 Gm./day
Mean arterial pressure	143 ± 21.5 mm. Hg (9%↓)	145 ± 16.4 mm. Hg (9%↓)	132 ± 17.3 mm. Hg (17%↓)

*By fourth month veratrum and hydralazine could be discontinued in 10 and 13 patients respectively.

hypertension presented here. The inability of ganglionic-blocking agents to control the accelerated phase of hypertension was not in keeping with prior experience in this clinic. Although toxic reactions were frequent with ganglionic-blocking agents, the accelerated phase of hypertension could usually be reversed. The poor results obtained in the patients presented here must be interpreted as indicating fulminating vascular disease. It was noteworthy, therefore, that the addition of chlorothiazide to ganglionic-blocking agents plus reserpine produced excellent results in all these patients. It would seem, therefore, that in the absence of uremia, such combination therapy should be instituted promptly when the accelerated phase of hypertension is present. Time need not be wasted in administering either drug separately.

The potentiation of the antihypertensive properties of mecamylamine by chlorothiazide made it necessary to reduce the dosage of mecamylamine to avoid severe postural hypotension. Although the reduced dose of mecamylamine avoided postural hypotension, undesirable side effects such as blurred vision, fatigue, and impotency still remained. It was noteworthy that when the accelerated phase of hypertension had been halted, i.e., papilledema had cleared, flame-shaped hemorrhages regressed, and the level of arterial pressure had been lowered, hydralazine or veratrum could be successfully substituted for mecamylamine.

It must be admitted that the continued good therapeutic response noted when these latter agents were substituted for ganglionic-blocking agents might not have been entirely due to these drugs. Studies in this laboratory have shown that acute reduction of arterial pressure with any agent in patients in an accelerated phase of hypertension has frequently been associated with a long period of hypotension, longer than can be accounted for by the action of the drug itself. Following acute therapy the arterial pressure frequently does not return to control levels for 6 to 8 weeks. Similarly, clinical experience attests to prolonged periods of hypotension following an acute insult to the circulation such as myocardial infarction or a cerebral vascular accident. It is as though a cycle has been interrupted or the barostat of arterial pressure has been set at a lower level. Whatever the reason for the continued good response in the patients presented here, long-term ganglionic-blocking therapy was seldom indicated. Reserving ganglionic-blocking therapy for the short-term treatment of the accelerated phase of hypertension will not only free the patient from uncomfortable side effects but will also insure sensitivity to ganglionic-blocking agents that may be life-saving at a later date.

Although chlorothiazide alone has no place in the treatment of severe hypertension, one might argue from the studies presented here that it is as effective as veratrum plus reserpine or hydralazine plus reserpine in patients with moderately severe hypertension. Its ease

TABLE 6.—*Moderate Hypertensive Group—30 Patients*

Dose	No treatment—1 mo.	Chlorothiazide—6 mos. (1 Gm./day)	Veratrum (15 pts.) or Hydralazine (15 pts.) + Reserpine (6 Mos.) (Veratrum—9-16 mg./day) (Hydralazine—200-300 mg./day) (Reserpine—0.25 mg./day)
Mean arterial pressure	160 ± 21.6 mm. Hg	143 ± 21.5 mm. Hg (9%↓)	145 ± 16.4 mm. Hg (9%↓)
Fundi	Grade II—30 pts.	II→III—1 pt.	II→III—2 pts.
Cong. failure	Minimal—2 pts.	Development of failure—1 pt.	Increase in failure—3 pts.
X-ray	Enlarged heart—16 pts.	Decrease in cardiac size—5 pts.	Decrease in cardiac size—1 pt.
ECG	Normal—11 pts. Old infarction—2 pts. Bundle-branch block—3 pts. L V H—15 pts.	Less L V H—3 pts.	Development L V H—2 pts. Less L V H—1 pt. Subendocardial ischemia—2 pts.
BUN	AVG 14 mg. per cent (9-26)	Increase 20 mg. %—1 pt.	Increase 15 mg. %—1 pt.

of administration—no need for individual titration of dosage, the almost complete absence of side effects, and the lack of drug resistance seem to make chlorothiazide the drug of choice in this regard. Since chlorothiazide alone was effective in only one half of the patients with moderately severe hypertension and, since the combination of chlorothiazide plus hydralazine or veratrum was effective in all of the patients with moderately severe hypertension, there would seem to be no indication to administer these agents separately. The potentiation of the antihypertensive properties of veratrum and hydralazine by chlorothiazide enables lower doses of these agents to be used, thus practically doing away with side effects.

Past experience with both hydralazine and particularly veratrum attests to the frequent development of drug resistance when these agents are used for long periods of time. It is important, therefore, that once a hypotensive effect had been attained with veratrum or hydralazine in the patients with moderately severe hypertension that these agents could be withdrawn and antihypertensive therapy continued with reserpine plus chlorothiazide. Again it might be argued that the continued good therapeutic effect in these patients was not a direct consequence of chlorothiazide plus reserpine but merely represented a quiescent phase of the hypertensive state. Those who think that reserpine administered by mouth possesses no antihypertensive properties would probably choose this latter interpretation.

It is suggested from these studies that the choice of the antihypertensive agent should change with the severity of the hypertensive state. Whereas ganglionic-blocking agents plus chlorothiazide are needed to control the accelerated phase of hypertension initially, once this phase has been controlled, less potent therapy may be substituted. It seems useful in this regard to divide antihypertensive therapy into 2 phases: initial and maintenance. Initial therapy in the accelerated phase of hypertension should include ganglionic-blocking agents, chlorothiazide, and reserpine. Following control of the accelerated phase (clearing of papilledema and retinal hemorrhages) veratrum or apresoline may be substituted for the ganglionic-blocking agents. In patients with moderately severe hypertension initial therapy consists of veratrum or apresoline plus chlorothiazide plus reserpine. Long-term maintenance therapy, which may be instituted when the arterial pressure has been stabilized for 2 or 3 months, consists of chlorothiazide plus reserpine.

Summary

Neither chlorothiazide alone nor ganglionic-blocking agents plus reserpine represented effective treatment in the 11 patients with severe hypertension studied here. The addition of chlorothiazide to ganglionic-blocking agents plus reserpine reversed the accelerated phase of hypertension in each of these patients. Once papilledema had cleared and retinal hemorrhages had regressed, it was possible to substitute hydralazine or veratrum for the ganglionic-blocking agents in these patients.

Chlorothiazide alone and veratrum or hydralazine plus reserpine were both found effective in controlling 50 per cent of the patients with moderately severe hypertension. The addition of chlorothiazide to either of these agents resulted in satisfactory control of the arterial pressure in all the patients with moderately severe hypertension. Once a hypotensive effect had been attained with veratrum or hydralazine, these agents could be withdrawn and antihypertensive therapy continued with reserpine plus chlorothiazide.

Summario in Interlingua

Ni chlorothiazido sol ni agentes de blocage ganglionic in combination con reserpina esseva efficace como medication in le 11 patientes con sever hypertension qui es hic studiate. Le addition de chlorothiazido a agentes de blocage ganglionic e reserpina reverteva le phase accelerate de hypertension in omne iste patientes. Post que le papilledema se habeva resolvite e post que le hemorrhagias retinal habeva regredite, il esseva possibile in iste patientes reimplaciar le agentes de blocage ganglionic per hydralazina o veratrum.

Chlorothiazido sol e veratrum o hydralazina in combination con reserpina se monstrava ambes efficace in le stabilisation del processo pathologic de 50 pro cento del patientes con hypertension de grados moderatemente sever. Le addition de chlorothiazido a iste agentes individual resultava in un satisfacente stabilisation del tension arterial in omne le patientes con hypertension de grados moderatemente sever. Post que un effecto hypotensive habeva essite establite per medio de veratrum o hydralazina, iste agentes poteva esser eliminate, e le therapia antihypertensive poteva esser continuate con reserpina in combination con chlorothiazido.

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Hence it sometimes happens that, when the lumen of some artery has been too long obstructed or ligated, the blood busies itself in opening a wider channel for its passage in this vessel, must drive and buffet all the more into the next ones, until it has considerably dilated them to give itself room.—Richard Lower, *Tractatus de Corde, 1669.*

A Hydrostatic Pressure Stocking for the Treatment of Ulcers due to Chronic Venous Insufficiency

By J. Edwin Wood, M.D.

Chronic venous insufficiency may be complicated by ulceration of the skin of the involved extremity. The ulcers appear to be caused by the prolonged elevation of venous pressure in the leg and the resultant edema. A device is described that counterbalances exactly the elevated pressure in the veins of the leg, regardless of the position of the patient. This hydrostatic pressure stocking prevents formation of edema without interfering with the flow of blood through the tissues. The use of this device in the treatment of ulcers due to chronic venous insufficiency is also described.

CHRONIC venous insufficiency[1] is a relatively common[2] syndrome that is caused by sustained elevation of the pressure in the veins of the dependent lower extremity. This high mean venous pressure results from inadequate closure of the valves in the veins during exercise of the muscles of the leg, especially if some of the venous channels are obstructed due to previous thrombophlebitis.[3-7] The high venous pressure is associated with an abnormally high capillary pressure, which is responsible in turn for the formation of edema in the tissues of the extremity.

The skin overlying these edematous areas may break down either following a minor injury or without apparent cause. Subsequently these small breaks in the skin tend to become large superficial ulcers. The question then arises as to whether the edema per se causes these ulcers by direct mechanical destruction of tissue or by separation of living cells from their immediate blood supply.[8, 9] Alternatively, the primary cause of the ulceration may be infarction of the skin due to diminished flow of blood. A decrease in the flow of blood would presumably occur in the absence of proper functioning of the venous valves, which allow a contracting skeletal muscle to propel blood out of the veins of the leg.[8] A further momentary reduction of blood flow and an increase in tissue pressure as well might occur with the sudden rise of venous pressure caused by coughing or the Valsalva maneuver.[9]

Ulcers due to venous insufficiency will eventually heal with prolonged continuous bed rest and elevation of the involved extremity. The essential effect of this therapy appears to be one of marked lowering of venous pressure in the legs and consequent dissipation of the edema. Such results suggest that a patient might avoid hospitalization if it were possible to prevent the formation of edema by maintaining very low local transmural venous and capillary pressures by adequate but not excessive external compression of the extremity. Excessive external compression would reduce transmural arterial pressure without a further reduction of transmural venous pressure,[10] thus diminishing the arterial-to-venous pressure gradient and reducing the volume of blood flowing through the tissues. Therefore, the pressure to be counterbalanced within the veins of the leg would be equal to that of a vertical column of blood (or for practical purposes, water) between any given point on the leg and the level of the right atrium, regardless of the position of the patient.[11] It is the purpose of this communication to describe a device that has been designed to produce counterpressure upon the extremity in just this manner. The use of this device in the treatment of ulcers due to chronic venous insufficiency is also described.

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FIG. 1. Lateral view of patient wearing hydrostatic pressure stocking.

METHODS

The primary component of the device* for compressing the leg was a knee-length, toeless stocking made of Nylon-cotton cloth. This stocking could be opened anteriorly with a zipper. It was fitted with laces along the lateral side to allow adjustment of its size. The size could also be adjusted across the dorsum of the foot. A watertight bladder was incorporated into the medial surface of the stocking. This bladder extended from the knee to a point just below the medial malleolus, and from the midline anteriorly to the midline posteriorly of the leg. A second smaller bladder was attached to the bladder in the stocking with 2 flexible rubber tubes 3 feet in length. There was an opening in the smaller bladder which was used to fill the entire system with 750 ml. of water. After the air was removed from the system this opening was closed. There were no valves in the system and the water could flow through the tubes from one bladder to the other. A strap was attached to the smaller bladder so that it could be suspended beneath the axilla (fig. 1).

Pressures were measured beneath the hydrostatic pressure stocking from a 3-by-1.5 cm., flat, water-filled, plastic capsule that had been placed between the skin and the stocking. This capsule was attached to a rigid plastic tube leading to a Statham P23D strain gage. Records were obtained with a Sanborn direct-writing oscillograph. Pressures were measured with the subject in the recumbent, sitting, and standing positions. Twelve points were used for these measurements in 3 subjects. These points were at the top, middle, and lower aspects of the leg anteriorly, posteriorly, laterally, and medially. The data are reported in terms of the difference between the observed and the predicted pressures. Pressures were predicted on the basis of the vertical distance between the capsule and the level of the center of the bladder in the axilla.

The hydrostatic pressure stocking was used as a sole means of therapy for 10 ambulatory patients with leg ulcers due to chronic venous insufficiency. The ulcer was covered with a sterile dressing held in place with gauze and adhesive tape. A knee-length elastic stocking was worn over this dressing, then the hydrostatic pressure stocking was placed on the leg and the smaller bladder was strapped beneath the axilla. The patient was instructed to wear the hydrostatic pressure stocking from the time that he got up in the morning until he retired at night. Some of the female patients wore an opaque cotton stocking over the hydrostatic pressure stocking while others preferred to wear slacks. Male patients wore an ordinary sock over the hydrostatic pressure stocking. Since the tubes that connected the 2 bladders were small and flexible, the patient could conveniently wear the entire device beneath his clothing. Special shoes were not required. The dressings were changed only as often as was necessitated by exudation from the ulcer surface.

RESULTS

Ten patients with chronic venous insufficiency associated with large ulcers of the skin of the leg were treated with the hydrostatic pressure stocking. All of the patients were urged to follow their usual daily routines.

Healing of the ulcers occurred in all of the patients. The rapidity with which the healing took place seemed to depend primarily upon the original size of the ulcer. The hydrostatic pressure stocking did not appear to shorten or lengthen the period of time

*Manufactured by the David Clark Company, Worcester, Mass.

required for healing of the ulcers compared with the period of time which might have been required for healing had the patient been hospitalized. Seven of the patients had had thrombophlebitis while the remaining 3 were apparently suffering from ulcers due exclusively to varicose veins. Initially, the ulcers were 3 to 8 cm. in diameter. The time required for complete epithelialization of the ulcer surfaces varied from 2 to 5 weeks. Four of the patients had experienced considerable pain in the region of the ulcer during dependency of their legs. The hydrostatic pressure stocking relieved this pain completely. In all cases, the gross edema was dissipated within 3 to 5 days after initiation of the therapy. The patients found the stocking to be more bulky and noticeable than an ordinary elastic stocking. They grew used to it after several days, however, and said that it did not interfere with their activities in any way.

The device was worn by a school instructor virtually continuously for a period of 2 years without interruption of his teaching duties. His difficulties were initiated by severe thrombophlebitis in the deep and superficial veins of the leg. After this, but prior to use of the hydrostatic pressure stocking, he had been hospitalized at yearly intervals for 6- to 8-week periods over a span of 6 years, because of repeated and extensive ulcer formation. All of the indicated surgical procedures to the venous system of his legs had been performed 3 or more years prior to initial use of the hydrostatic pressure stocking. During the subsequent 2 years when he wore the stocking it was not necessary to hospitalize him. Two ulcers on one leg healed completely with this form of therapy. Following this it was necessary for him to be without the device on 2 occasions for 3-week periods and in each instance an ulcer appeared but healed again upon resumption of therapy.

A second patient continued to work as a cook in a restaurant while wearing the hydrostatic pressure stocking. His job required that he stand for most of the day. An ulcer 3.5 cm. in diameter, due apparently to varicose veins, healed during 4 weeks of treatment with the stocking. Then he stopped wearing the stocking and elected to defer surgical therapy of his varicose veins. When a second ulcer 0.5 cm. in diameter occurred 11 months later, he was hospitalized for ligation and stripping of his varicose veins.

A third patient was an obese, elderly woman who worked in a nursing home. She had had a deep ulcer 7 cm. in diameter on the anterior surface of her leg for a period of over 5 years. The ulcer was due to varicosities and previous thrombophlebitis. It had been treated with various forms of compression but to no avail. She had never been hospitalized however. The ulcer healed completely during a period of 5 weeks' treatment with the hydrostatic pressure stocking. This patient had extremely large legs as a result of the obesity and edema. It was possible to adjust the stocking to fit her leg without special tailoring.

The remaining patients in the series had had ulcers of the lower extremity for relatively short periods of time. Their course of treatment with the hydrostatic stocking was uneventful. It was of interest to observe that secondary infection of the ulcers, even when severe, cleared promptly with this form of therapy. As noted above, antibiotic or other local applications were not used.

All of the patients studied had subcutaneous fibrosis, which was evident after dissipation of the edema. The extent of this fibrosis varied but it was marked in 4 of the patients. As with other forms of therapy for these ulcers, extensive subcutaneous fibrosis seemed to be associated with a slower rate of healing of the skin.

All of the patients apparently followed instructions faithfully as to the use of the hydrostatic pressure stocking.

Pressures beneath the hydrostatic pressure stocking relative to those predicted from the level of the bladder in the axilla, averaged +1.2 (range −5.8 to +6.4) cm. of water meas-

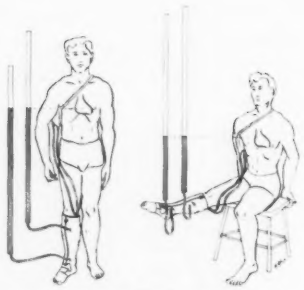

FIG. 2. Diagrammatic illustration of the results of pressure measurements beneath the hydrostatic pressure stocking from 2 points with the subject in 2 positions.

ured at 12 points beneath the stocking in the recumbent, sitting, and standing positions. The results obtained from 2 points beneath the stocking, in 2 positions are illustrated (fig. 2). The pressures were attained in 15 to 30 seconds with each change of position of the subject.

The durability of the stocking was outstanding in that the first patient referred to above demonstrated that it could be worn daily for at least a year without developing serious defects. Since numerous modifications of the stocking were made from the time he first began its use, he did not wear any single stocking for longer than 1 year. Three of the stockings have been filled with water for 2½ years and have shown no evidence of leaking.

DISCUSSION

Patients with large ulcers of the leg caused by chronic venous insufficiency often have to be hospitalized before healing can be achieved. These ulcers apparently occur as a result of the high venous pressures in the leg associated with the erect posture. The high pressure is not lowered significantly by walking, especially if the chronic venous insufficiency has resulted from previous thrombophlebitis.[3-7] Presently available methods for treatment of such patients on an ambulatory basis involve the application of some form of compression that imparts essentially a constant pressure to the ulcer. Occasionally, such methods of treatment are quite effective, but in general the results are unpredictable. The reason for this variation undoubtedly lies in the difficulty of selecting or applying a single pressure to the extremity that would be reasonably effective in all situations. For example, the external pressure needed to counterbalance the venous pressure that occurs at the level of the ankle of a patient 6-feet tall in the standing position would be approximately 130 cm. of water. Ordinary elastic compression imparts about 25 cm. of water pressure to the tissues. If a pneumatic cuff[12] were used to produce the needed counterpressure of 130 cm. of water (96 mm. Hg), the patient would experience a significant decrease in blood flow to the foot when he assumed the sitting or supine position. This factor would be especially important if the patient were also suffering from arterial insufficiency. The presence of arterial insufficiency should lead the physician to use any form of external compression cautiously. However, a pressurizing device that adjusts itself to counterbalance exactly the venous pressure of the leg is the safest of the available methods for use in this circumstance. This form of compression reduces the effective local arterial pressure to the same extent that it reduces the effective local venous pressure, so that the effective gradient of pressure from artery to vein would not be altered. If the pressure used on the leg greatly exceeded that needed to counterbalance local venous pressure, then it would result in a further decrease in effective local arterial pressure without a further decrease in effective local venous pressure so that the arterial-to-venous gradient of pressure would be reduced and consequently a reduction of blood flow would occur.[10]

It is evident that it would be theoretically advantageous to pressurize the leg of a patient with chronic venous insufficiency and ulceration of the skin from a column of water whose height is governed by the position of the patient. It was possible to incorporate a hydrostatically pressurized bladder into a stocking that could be worn for long periods of time without serious inconvenience to the patient. In fact several patients continued to be employed in full-time occupations during treatment with this hydrostatic pressure

stocking. All of the patients treated with this device had complete healing of the ulcers. In some no further surgical procedures were indicated while others entered the hospital for definitive corrective surgery to the veins as soon as the ulcers were healed.

The pressures actually reflected onto the surface of the leg by the hydrostatic pressure stocking were, with minor variations, those that were predicted for the position of the patient. Venographic studies of the lower extremity have shown that external local compression of the leg results in a narrowing of deep as well as superficial veins.[13] Direct measurements of tissue pressure[14] and studies of changes of venous volume with external compression[10, 15] have also indicated that the pressure is transmitted to the deep as well as the superficial tissues.

The results of the studies here reported suggest that edema per se plays a decisive role in the perpetuation of the ulcers of chronic venous insufficiency. The primary effect of the hydrostatic pressure stocking would seem to be one of maintaining a low transmural pressure within the veins and capillaries of the leg with a resultant diminution of edema formation. It is at least theoretically possible, however, that blood flow was improved with use of this device. The lower effective venous pressure and the associated lower venous volume[15] might have allowed the leaflets of the small number[16] of venous valves to come into apposition, so that the normal "venous heart" mechanism operated to some extent to remove blood from the exercising calf. Finally, the brief rises of venous pressure that occur with coughing or with the Valsalva maneuver[9] might have been partially counterbalanced by the hydrostatic pressure stocking.

Summary

A device is described that reflects counterpressure onto the surface of the leg in such a way that the pressure is equivalent to that of a vertical column of water between any point on the leg and the level of the right atrium regardless of the position of the patient. This device, the hydrostatic pressure stocking, could be conveniently worn by patients.

Ten patients with ulcer of the skin of the leg due to chronic venous insufficiency used the hydrostatic pressure stocking as a sole means of therapy while pursuing their usual daily activities. All of the ulcers healed completely with this treatment. The rate of healing was as rapid as might have been expected with complete bedrest and elevation of the extremity.

The hydrostatic pressure stocking does not obviate the necessity of indicated surgery to the local venous system. This device may serve as a useful adjunct to surgery in that an ulcer can be healed prior to entrance into the hospital, thus reducing the chances of subsequent wound infections. The hydrostatic pressure stocking appears to be of special value to patients who have chronic venous insufficiency with repeated formation of ulcers, when all forms of surgical therapy have been exhausted.

The results of these studies suggest that the primary value of the hydrostatic pressure stocking in the treatment of ulcers of chronic venous insufficiency is prevention of the formation of edema. Improved blood flow and counterbalancing of sudden rises of local venous pressure with coughing cannot be ruled out as additional beneficial effects however.

Acknowledgment

The author wishes to express his appreciation to Mr. John E. Flagg and to the David Clark Company for their aid in the design and for the construction of the hydrostatic pressure stocking.

Summario in Interlingua

Es describite un dispositivo que reflecte un contrapression contra le superficie del gamba in un tal maniera que su effecto es le equivalente del effecto pressori de un columna de aqua inter non importa qual puncto super le gamba e le nivello del atrio dextere, sin reguardo al postura occupate per le patiente. Iste dispositivo, le calcea de pression hydrostatic, pote esser portate per le patiente sin inconveniente.

Dece patientes con ulceres cutanee al gamba causate per chronic insufficientia venose usava le calcea de pression hydrostatic como

le exclusive mesura therapeutic durante que illes esseva ingagiate in lor usual activitates quotidian. Sub iste tractamento omne le ulceres se sanava completemente. Le rapiditate del sanation esseva lo que on haberea expectate sub le conditiones de allectamento complete con elevation del extremitate.

Le calcea de pression hydrostatic non elimina le necessitate de chirurgia local in le systema venose quando un tal es indicate. Illo pote esser usate como adjuncto benefic al chirurgia, in tanto que un ulcere pote esser sanate ante le hospitalisation del patiente de maniera que le risco de subsequente infectiones del vulnere es reducite. Il pare que le calcea de pression hydrostatic es de valor special in le caso de patientes con chronic insufficientia venose in qui il ha repetite formation de ulcers e in qui omne formas de therapia chirurgic ha essite exhaurite.

Le resultatos de iste studios suggere que le prime valor del calcea de pression hydrostatic in le tractamento de ulceres causate per chronic insufficientia venose es le prevention de omne formation de edema. Tamen, un melioration del fluxo de sanguine e le equalisation de subite augmentos de local pression venose quando le patiente tussi non pote esser negate como benefic effectos additional.

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Effect of Heart Irregularity on Left Ventricular and Arterial Peak Systolic Pressures in Aortic Stenosis

By W. S. Breall, M.D., and A. B. Shaffer, M.D.

In aortic stenosis, systemic arterial peak systolic pressure may remain relatively steady in the face of marked, arrhythmia-induced, variations in left ventricular peak systolic pressure. A possible basis for this phenomenon is presented. It is suggested that beat-to-beat variations in the systolic pressure gradient across the aortic valve region may not always reflect variations in stroke volume.

UNDER most circumstances when the pulse is irregular, systemic arterial systolic pressure closely mirrors the variations in left ventricular systolic pressure although the 2 are not necessarily identical. By contrast, left heart catheterization of patients with aortic stenosis, in whom the pulse was irregular, revealed exaggerated beat-to-beat variation in left ventricular peak systolic pressure, with little variation in simultaneously recorded systemic arterial peak systolic pressure. The purpose of this communication is to call attention to this phenomenon, and to provide a possible explanation.

Material

All left heart catheterization data (posterior percutaneous approach[1] and data obtained at the time of cardiac surgery were reviewed. Cases demonstrating beat-to-beat variations in left ventricular systolic pressure with simultaneously recorded radial, brachial, or aortic pressure were selected for analysis. Variations were due to arrhythmias or were respiratory. Arrhythmias included premature beats, atrial fibrillation, and sinus arrhythmia. Aortic stenosis was present in some cases, absent in others. The cases selected for presentation are representative.

Results

Figures 1 and 2 depict simultaneously recorded left ventricular and systemic arterial pressure pulses in 2 cases of aortic stenosis. Noteworthy, particularly in figure 1, are the markedly variable left ventricular peak systolic pressures and the much less variable arterial peak systolic pressures. The systolic pressure gradient across the aortic valve region is correspondingly variable. In contrast, in the absence of aortic stenosis (fig. 3), systemic pressure mirrors left ventricular pressure with great fidelity.

The relationship of ventricular and arterial peak systolic pressure level to previous cycle length has been plotted as a pressure-time curve for each of cases 1 and 3 in figures 4 and 5 respectively. The expected dependence of left ventricular peak systolic pressure level on previous cycle length is clearly indicated in both figures. Noteworthy is the flat arterial curve in figure 4 in the presence of relatively severe aortic stenosis, contrasting with figure 5 in which, stenosis being absent, the arterial curve parallels the ventricular curve.

Discussion

The left ventricular pressure-time curves in figures 4 and 5 are of a contour one would expect from the classic observation of dependence of ventricular systolic pressure on end-diastolic volume.[2] In the arrhythmias under discussion, a greater diastolic filling time presumably acting through increased end-diastolic volume, results in a more forceful ventricular contraction. The force of ventricular contraction is a major determinant of left ventricular systolic pressure. In the normal heart, the left ventricle and major arteries act as a common chamber during systole, pressures being approximately equal al-

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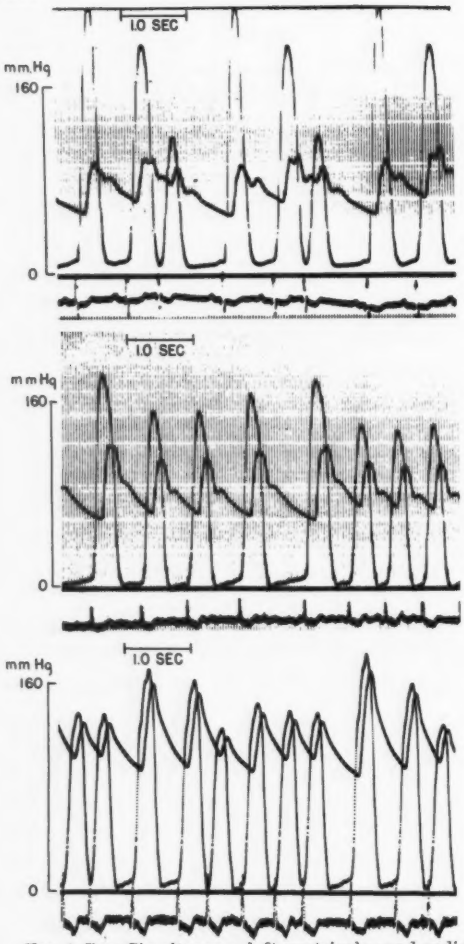

FIG. 1 *Top.* Simultaneous left ventricular and radial arterial pressure pulse curves and electrocardiogram (lead II) in a patient with aortic stenosis (case 1), showing atrial premature contractions followed by pauses. Note the marked variation in left ventricular peak systolic pressures with almost constant radial arterial peak systolic pressures. The radial arterial systolic pressure tends to be highest in beats terminating normal intervals rather than in association with highest left ventricular systolic pressures, and is lowest in association with premature beats. Note also variations in radial arterial pulse contour.

FIG. 2 *Middle.* Simultaneous left ventricular and radial arterial pressure pulse curves and electrocardiogram (lead II) in a patient with atrial fibrillation and aortic stenosis (case 2).

FIG. 3 *Bottom.* Simultaneous left ventricular and aortic pressure pulse curves and electrocardiogram (lead II) in a patient with atrial fibrillation and no aortic stenosis (case 3). Note the parallel variations in aortic and left ventricular peak systolic pressures.

though in the peripheral vessels some variation occurs due to deformation in transmission of the pulse. When aortic stenosis is present, the left ventricle and systemic arterial tree can no longer, from the physiologic point of view, be considered as a single chamber in systole. The severity of the stenosis is an important determinant of the systolic pressure gradient across the aortic valve region. This pressure gradient, however, varies not only with the degree of stenosis but apparently also with the square of the stroke volume. While it is evident from the foregoing that relatively small changes in stroke volume may markedly affect the gradient, consideration of the hemodynamics in individuals without aortic stenosis would lead to the conclusion that arterial systolic pressure in aortic stenosis should still mirror left ventricular systolic pressure but with less marked variations as the gradient widens or narrows from beat to beat in relation to changes in stroke volume. Case 1 (figs. 1 and 4) illustrates how varitions in left ventricular peak systolic pressure as great as 120 mm. Hg may be almost totally unreflected in the systemic arterial pulse, and suggests that other factors are active.

In aortic stenosis, left ventricular peak systolic pressure is determined primarily by the force of ventricular contraction and the resistive force of the stenotic valve. The assumption appears reasonable that the stenotic resistive force is dependent upon the force of left ventricular contraction; the greater the contracting force, the greater being the resistive force. Systemic arterial peak systolic pressure would be determined primarily by the force of ventricular contraction minus the stenotic resistive force. Should the resistive force vary with the contracting force, a possible result might be partial or almost complete failure of arterial peak systolic pressure to reflect variations in left ventricular systolic pressure, as best seen in figure 1. Related to this is the effect of graded severity of stenosis on stroke volume. The latter may be expressed as mean velocity of ejection × cross sectional area of the valve orifice in systole.

If aortic stenosis exceeds a certain critical severity, variations in force of ventricular contraction may no longer be able to influence velocity of outflow. It then follows that stroke volume will vary only with the duration of ejection. While variations in duration of ejection do occur, they are small and could not be expected greatly to influence stroke output from beat to beat in these circumstances. Thus, the almost complete lack of variation in arterial systolic pressure levels could be attributed in part to a relatively fixed stroke output, and the pressure gradient might then vary widely while the stroke output remains relatively fixed. A lack of correlation between pressure gradient and stroke volume would result when the circumstances illustrated in figure 1 exist.* Other factors contributing to systemic arterial systolic pressure level, such as peripheral vascular resistance, volume-elasticity characteristics of the systemic arterial tree, etc., are well known,[3] and will not be further detailed here. There appears to be little reason for assuming that their quantitative contributions to beat-to-beat variations in arterial systolic pressure in the presence of aortic stenosis differ in any important respect from the normal.

When a more variable arterial peak systolic pressure is noted (fig. 2), one might assume either a less severe degree of stenosis or alternatively, a less rigid form of stenosis, in which the stenotic opening alters in size with changes in the force of ventricular contraction.

While the practical importance, in the assessment of aortic stenosis, of a systolic pressure gradient across the aortic valve region cannot be denied, particularly when flow past the aortic valve can be taken into account, the above observations cast some doubt on the assumed simple relationship between pressure gradient and stroke volume. Further evaluation will have to await the development of a technic for measuring beat-to-beat variations in stroke volume in man.

An incidental observation in case 1 should be mentioned. Figure 1 shows that the contour of the systemic arterial pulse is variable, although the pressure level changes but little. As left ventricular peak systolic pressure increases, the arterial pressure pulse becomes more characteristic of aortic stenosis. Ar-

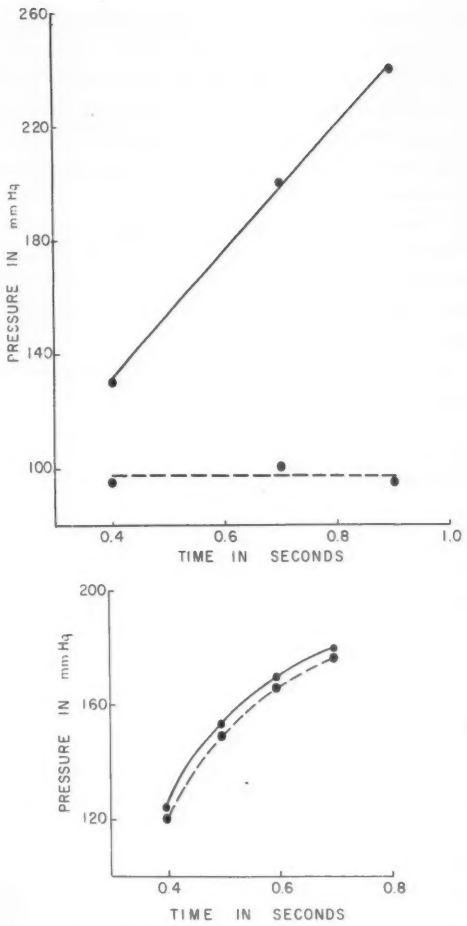

FIG. 4 *Top.* Systolic pressure-time curves for the left ventricle (*solid line*) and radial artery (*dashed line*) in aortic stenosis (case 1).

FIG. 5 *Bottom.* Systolic pressure-time curves for the left ventricle (*solid line*) and aorta (*dashed line*) with no aortic stenosis (case 3).

*Expressed in terms of external work of the ventricle ($EW = PQ + Mv^2/2g$, where EW = external work, P = ventricular mean systolic pressure, Q = stroke volume, M = mass of blood moved, v = velocity and g = gravitational constant), if v and therefore Q and M are maximum and fixed, a rise in P will determine increase in EW which is entirely isovolumic and therefore unrelated to flow.

terial pulse contour has been related in a general way, both experimentally[4] and clinically,[5] to the severity of stenosis. Therefore, the present observation suggests that the degree of stenosis is relatively exaggerated during certain beats. While it is possible that variations in stroke output might be, in part, the basis for this variation, the idea that the resistive force opposing outflow is in a sense variable, depending on the force of ventricular contraction, is a more attractive hypothesis.

The possibility exists that a relatively fixed systemic arterial systolic pressure level in the presence of an irregular pulse may be an additional clinical reflection of severe aortic stenosis.

Summary

In aortic stenosis with an irregular pulse, a relatively less variable or almost constant peripheral arterial peak systolic pressure is described in association with marked variation in left ventricular systolic pressure. Possible mechanisms for this phenomenon are discussed.

Acknowledgment

We are indebted to the Attending Physicians for permitting us to make use of data on their patients, and to Dr. Louis N. Katz for his advice in the preparation of this report.

Summario in Interlingua

In stenosis aortic con irregularitates del pulso, un relativemente minus variabile o quasi constante maximo del tension systolic periphero-arterial es describite in association con marcate variationes del tension systolic sinistro-ventricular. Mechanismos possibile de iste phenomeno is discutite.

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I think that knowledge of every kind is useful in proportion as it tends to give people right ideas, which are essential to the foundation of right practice, and to remove wrong ideas, which are the no less essential foundations and fertile mothers of every description of error in practice. And inasmuch as, whatever practical people may say, this world is, after all, absolutely governed by ideas, and very often by the wildest and most hypothetical ideas, it is a matter of the very greatest importance that our theories of things, and even of things that seem a long way apart from our daily lives, should be as far as possible true, and as far as possible removed from error.—Thomas H. Huxley. *American Address with a Lecture on the Study of Biology*. London, MacMillan and Co., 1877, p. 142.

Gallop Rhythm of the Heart

II. Quadruple Rhythm and its Relation to Summation and Augmented Gallops

By JOSEPH GRAYZEL, M.D.

The 2 fundamental types of gallop are ventricular gallop and atrial gallop. Adequate cardiac acceleration modifies these gallops and may produce a summation gallop, an augmented ventricular gallop, or an augmented atrial gallop. The summation and augmented gallops were examined and their relation to the 2 fundamental gallops was quantitated. The cardiac rate at which summation and augmentation occur is unique. A graph and 2 corresponding equations were derived which relate the summation cardiac rate and corresponding cycle length to familiar electrocardiographic and phonocardiographic intervals.

GALLOP rhythm has been defined as a "mechanical hemodynamic event associated with a relatively rapid rate of ventricular filling and characterized by a ventricular bulge and a low-frequency sound."[1] From this definition it follows that the cardiac gallop is a diastolic event. Of the 5 divisions of diastole—protodiastole of Wiggers, isometric ventricular relaxation, rapid ventricular filling, slow ventricular filling, and atrial contraction—a relatively rapid rate of ventricular filling occurs during 2 periods, the rapid-filling phase, which follows immediately upon opening of the atrioventricular valve, and the atrial phase, which follows contraction of the upper chamber. Two corresponding types of gallop exist. These are the rapid-filling (or ventricular) gallop and the atrial gallop, respectively. Both types of gallop are ventricular phenomena and each may be generated in either ventricle. Therefore, it is desirable to specify whether a gallop originates from the right or left side of the heart.

Gallop may occur at any heart rate. Associated mechanical aspects of the gallop have been recorded with the electrokymogram,[2] slit roentgenkymogram,[3] ballistocardiogram,[4,5] and apex cardiogram.[1]

Ventricular gallop appears indicative of diastolic overload. It occurs with an abnormal relation between the rate of rapid filling and the ventricle's ability to accommodate its increasing diastolic volume. The wave of rapid left ventricular filling is increased in mitral insufficiency, in which left atrial volume is large, the atrial pressure is high, and mitral stenosis is not of a degree to restrain the rate of flow from atrium to ventricle.

In aortic insufficiency the regurgitant blood stream augments left ventricular filling and the total rapid-filling wave exceeds that normally present.

Left-to-right shunts at the ventricular level or between the great vessels result in increased left ventricular diastolic filling and stroke volume. Examples are interventricular septal defect, patent ductus arteriosus, and aortic-pulmonary window.

Interatrial septal defect increases diastolic filling of the right ventricle and rapid-filling gallop of the right ventricle may occur.

More common than ventricular gallop due to an increased filling wave is ventricular gallop due to altered accommodation during the volume changes of diastole. The most frequent cause is heart failure, in which the ventricle is dilated and myocardial tone is poor.

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Left ventricular gallop occurs 0.15 second after the onset of the second heart sound.[1, 4, 6, 7] An exception is mitral insufficiency, in which this gallop begins 0.10 second after the second heart sound[1] due to earlier opening of the mitral valve when left atrial pressure is elevated, ending a shortened period of isometric ventricular relaxation.

Atrial gallop appears indicative of systolic ventricular overload. It is generated on the left side of the heart in essential hypertension and aortic stenosis, and on the right side in pulmonary hypertension of varied etiology and in pulmonic stenosis.

When atrial gallop is present in essential hypertension, there is invariably evidence of left ventricular hypertrophy, either from physical examination, roentgenograms, or the electrocardiogram.[1, 8] The atrial gallop will often persist when the blood pressure in a known hypertensive person is within normal range. This observation suggests that the ventricular changes, rather than the elevated blood pressure per se, are essential for the production of this presystolic gallop. In the known hypertensive person the presence of an atrial gallop warrants a diagnosis of hypertensive heart disease.

The interval from the onset of the P wave of the electrocardiogram to the left atrial gallop is 0.14 second.[1, 6, 9] The inaudible vibrations of mechanical atrial contraction occur earlier than the atrial gallop. Many of the atrial sounds heard in various degrees of heart block occur later than true atrial gallop.

Quadruple rhythm denotes the presence of 4 heart sounds. The special case of concern here is quadruple rhythm due to the occurrence of both left ventricular and left atrial gallops in addition to the normal first and second heart sounds.

As the heart rate increases, the cycle length decreases, principally at the expense of diastole. More specifically, the period of slow ventricular filling is shortened and even totally eliminated with tachycardia of sufficient degree. At this point a slight additional increase in rate results in superposition and summation of the rapid-filling phase and atrial contraction (summation phenomenon). When both the rapid-filling and atrial gallops are present, they are superimposed as summation occurs. The resulting single, intense gallop is called summation gallop. The single sound is usually much louder than would be obtained from simple addition of the 2 component sounds; this gives the impression that the intensities are multiplied rather than summed as the name implies.

When the summation gallop occurs, mechanical and auscultatory aspects of the 2 component gallops appear summated. There is summation of the respective ventricular thrusting forces as well as summation of the sounds.

A rapid ventricular filling gallop is greatly intensified when a previously silent phase of atrial contraction is superimposed upon it by an increased heart rate. The single ventricular gallop intensified by this mechanism is augmented both mechanically and acoustically, and is called augmented ventricular gallop. Similarly, an atrial gallop superimposed upon a silent period of rapid ventricular filling is intensified and is called augmented atrial gallop. Thus, the mechanism of the augmented gallop and the true summation gallop is similar in that superposition of the rapid ventricular filling period and the period of atrial contraction is essential to both.

The intensity of an augmented gallop and the loudness of the true summation gallop make these easily audible and probably account for the repeated statement that a gallop is only heard during tachycardia.

A single loud gallop sound present during tachycardia may be either an augmented gallop or a true summation gallop. The distinction can be made only when the heart rate is slowed. The summation gallop will change to a quadruple rhythm at the slower rate. The augmented gallop will only decrease in intensity, the sound remaining single. If an augmented ventricular gallop is present, the sound will retain its relation to the

second heart sound and remain in early diastole. If an augmented atrial gallop is present, the sound will retain its relation to the P wave and remain presystolic.

Method and Materials

Phonocardiograms were recorded simultaneous with the electrocardiogram and apex cardiogram on a Sanborn Twin-beam at a paper speed of 75 mm. per second with vertical time lines at 0.04 second. The patients were in the supine position.

The method for recording local precordial movements has been described previously.[1] An upward deflection on the apex cardiogram represented a forward movement in the region of maximum cardiac pulsation.

Observations on 5 patients with gallop sounds and the pertinent clinical details are presented. Quadruple rhythm due to the presence in each cardiac cycle of both the rapid-left-ventricular-filling gallop and the left atrial gallop was recorded in 2 patients. The various time intervals associated with these gallops have been included among previous observations.[1] An augmented gallop or a true summation gallop was recorded in 3 patients.

Case Reports

Case 13

E.C. was a 52-year-old Negro with a history of progressive exertional dyspnea for 2 years and recent orthopnea. On physical examination the blood pressure was 180/110, there was grade-II hypertensive retinopathy, and rales were present at both lung bases. The heart was moderately enlarged, and no murmurs were audible. Excursions at the point of maximum cardiac pulsation were complex: a prominent early diastolic bulge was present as well as a presystolic bulge, the latter giving the impression of a double systolic impulse. Upon auscultation the normal first and second heart sounds were easily identified. Two low-pitched sounds were present in diastole. The first occurred soon after the second heart sound and corresponded in timing to the early diastolic, left ventricular bulge. The second low-pitched sound occurred with the presystolic bulge.

A phonocardiogram (fig. 1) showed the low frequency (fundamental 25 c.p.s.) early diastolic sound occurring 0.16 second after the second heart sound. The presystolic sound was also of low frequency (fundamental 25 c.p.s.) and followed the P wave by 0.12 second. Both diastolic sounds occurred simultaneously with a prominent ventricular bulge on the apex cardiogram, indicating the presence of rapid-filling gallop and atrial gallop, respectively.

Comment. Atrial gallop of the left heart, which is associated with systolic overload of the left ventricle, was caused in this patient by essential hypertension. The electrocardiogram was normal. Rapid-filling gallop, which accompanies diastolic overload, in this case was the result of heart failure.

Case 14

W.O.H. was a 24-year-old white man who had experienced recurrent episodes of acute hemorrhagic glomerulonephritis since childhood. In 1954 hypertension and impaired renal function were present. In 1958 he was hospitalized for severe heart failure and terminal renal failure. At this time the blood pressure was 180/110. There was grade-III hypertensive vascular retinopathy. Rales were heard over both lung fields. The heart was enlarged to the anterior axillary line. No murmurs were audible. The cardiac pulsations were undulating in character and suggested myocardial disease. A relatively distinct forward movement could, however, be consistently discerned in early diastole and was more distinct than the systolic impulse. Coincident with this early diastolic bulge was a low-pitched sound, loudest near the apical region. A faint presystolic sound of low pitch was also heard at the apex, but was loudest in the left fourth interspace. The neck veins were distended, the liver was tender and enlarged, and there was 4-plus pitting edema of the legs and ankles.

The hematocrit value was 22 per cent and the blood urea nitrogen was 228 mg. per 100 ml. The electrocardiogram was within normal limits. A phonocardiogram recorded both diastolic sounds with fundamental frequencies of 35 and 50 c.p.s., respectively. The early diastolic sound was loudest near the apex (fig. 2*B*) and the presystolic sound was loudest in the left fourth interspace (fig. 2*A*). The apex cardiogram (fig. 2*C*) illustrated the undulating cardiac movement felt through the chest wall. However, a prominent early diastolic bulge appeared consistently, simultaneous with the early diastolic sound, and indicated the presence of a rapid-filling gallop. A frank presystolic bulge simultaneous with the atrial presystolic gallop sound was not demonstrable. Presumably, the presystolic undulating wave occurring with the sound was in part due to the gallop bulge.

Comment. The atrial presystolic gallop in this case reflected hypertensive heart disease resulting from hypertension of 4 years' duration, secondary to renal disease. Left ventricular hypertrophy was confirmed at postmortem examination, although electrocardiographic evidence of hypertrophy was not present. The rapid-filling gallop reflected the

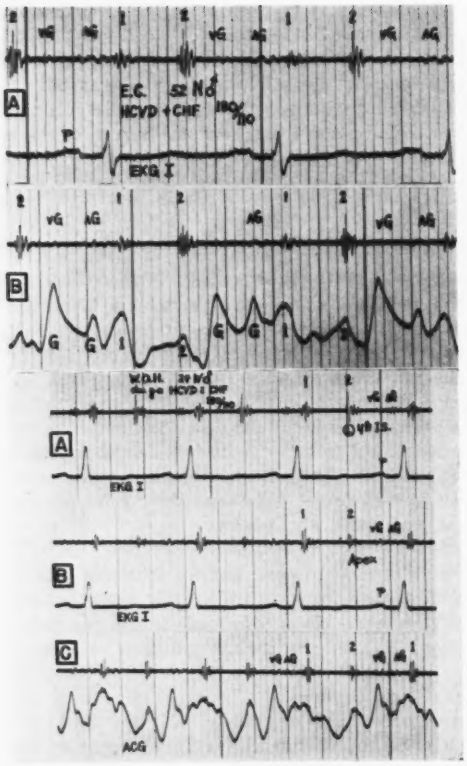

FIG. 1 *Top.* Case 13. Phonocardiogram with simultaneous electrocardiogram, lead I (*A*), and apex cardiogram (*B*). The ventricular gallop (*vG*) occurs in early diastole. The presystolic atrial gallop (*aG*) follows the P wave but precedes the QRS complex. The first and second heart sounds are indicated by *1* and *2*, respectively. Each gallop sound (*vG* and *aG*) occurs simultaneously with a gallop bulge (*G*). In the second cycle in *B* a definite ventricular gallop sound was not recorded though the gallop was still present, as evidenced by a prominent precordial movement (*G*) in early diastole.

FIG. 2 *Bottom.* Case 14. *A*. Phonocardiogram in the fourth interspace left of the sternum and simultaneous electrocardiogram, lead I. The presystolic atrial gallop sound is prominent while the early diastolic ventricular gallop sound is very soft. *B*. Phonocardiogram at the cardiac apex and simultaneous electrocardiogram, lead I. In this location the ventricular gallop sound is louder than the atrial gallop sound. *C*. Simultaneous phonocardiogram and apex cardiogram. A sharp, prominent precordial bulge consistently occurs with each ventricular gallop sound. The atrial gallop sound is not accompanied by such a definite movement. The undulating wave at the time of the atrial gallop sound is probably due, in part, to the gallop bulge.

myocardial failure. It is commonly found, as in this case, that the atrial and ventricular gallop sounds are loudest in different areas of the precordium.

Case 15

L.L. was a 51-year-old obese Negro with known hypertension for 6 years and symptoms of congestive heart failure during the 3 years prior to this hospitalization for severe dyspnea, orthopnea, and massive edema.

The blood pressure was 192/130 with 12 mm. of systolic alternation. The minute pulse rate was 107. The ocular fundi showed grade-II hypertensive vascular changes. There were basilar rales in both lungs. The heart was enlarged to the anterior axillary line. No murmurs were audible, but 3 heart sounds were present: the first sound was soft, and the second sound and the extra diastolic sound were of equal intensity, but the latter was of low pitch. The chest wall was obese and a diastolic ventricular bulge could not be detected. The neck veins were distended and there was 4-plus pitting edema of the ankles, legs, and lower thighs. An electrocardiogram showed left axis deviation but no evidence of hypertrophy.

A phonocardiogram (fig. 3) demonstrated the diastolic sound of low frequency (fundamental 50 cycles per second) which occurred 0.15 second after the second heart sound and 0.13 second after the P wave of lead II. A satisfactory apex cardiogram could not be recorded through the obese chest wall.

Comment. The diastolic gallop sound followed the second heart sound by the proper interval for a rapid-filling left ventricular gallop and followed the P wave by the proper interval for a left atrial gallop. It is justified to conclude that the summation phenomenon was present. Subsequently, with a minute cardiac rate of 90, quadruple rhythm was present due to the occurrence of the ventricular and atrial gallops separately with each cardiac cycle. Therefore, the single diastolic sound recorded at a heart rate of 107 represented a true summation gallop as opposed to an augmented gallop as defined above. Atrial gallop in this hypertensive patient indicated myocardial hypertrophy. Ventricular gallop was the result of diastolic ventricular overload secondary to heart failure.

Case 16

W.I. was a 32-year-old Negro who had been observed for 2½ years with congestive heart failure. The clinical impression was "idiopathic myocardial failure," commonly seen in young Negroes. At this time the blood pressure was 120/70 and the minute pulse 108. Basilar rales were heard bilaterally. The heart was enlarged well to the

interior axillary line. A blowing grade-II apical systolic murmur was audible. A loud low-pitched diastolic sound was present and coincided with a relatively large forward movement of the region of maximum cardiac pulsation. The liver descended 1 fingerbreadth below the right costal margin and was tender. There was 1-plus ankle edema. An electrocardiogram was within normal limits.

A phonocardiogram (fig. 4*A*) demonstrated the gallop sound occurring 0.16 second after the second heart sound and 0.13 second after the P wave of lead II. The simultaneous ventricular bulge on the apex cardiogram was striking (fig. 4*B*).

Comment. The time interval from the second heart sound to the gallop was appropriate for a rapid-filling left ventricular gallop. The interval from the P wave to the gallop was appropriate for a left atrial gallop. Thus, the summation phenomenon is present. At a slower cardiac rate the gallop remained single, was of less intensity, and maintained its relation to the second heart sound. The record shown (fig. 4) is therefore, an example of an augmented ventricular gallop.

Case 17

J.H.S. was a 35-year-old white man who had been observed for 2 years with heart failure. The clinical impression was "idiopathic myocardial failure." There was never any evidence of hypertension or coronary artery sclerosis. The blood pressure was 105/90 and the minute pulse 104. The ocular fundi were unremarkable. Rales were heard at both lung bases. The heart was moderately enlarged. A very low pitched diastolic sound was audible and coincided with a prominent apical bulge. This gallop sound was the loudest of the 3 heart sounds. The first heart sound was particularly soft. The neck veins were slightly distended and there was 3-plus ankle edema. An electrocardiogram showed complete left bundle-branch block.

A phonocardiogram (fig. 5*A*) demonstrated a gallop sound of high intensity and low frequency (fundamental 45 c.p.s.), which occurred simultaneously with the sharp spike on the apex cardiogram (fig. 5*B*).

Comment. The simultaneous sharp ventricular bulge established the diastolic sound to be a gallop. It occurs 0.13 second after the second heart sound, which is slightly less than the mean value for this interval but still appropriate for a left ventricular gallop. The P wave was lost in the preceding T wave with a P-R interval of 0.20 to 0.22 second. The interval between the P wave and the gallop was in the range appropriate for a left atrial gallop. The great intensity of the gallop compared to the first and second heart sounds further supports the conclusion that the summation phenomenon was present. This patient was not observed at a slower cardiac rate and we are therefore unable to say whether the gallop was a true summation gallop or an augmented gallop.

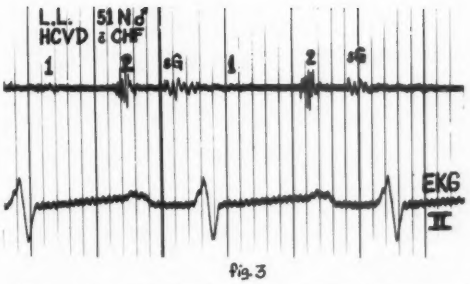

FIG. 3. Case 15. Simultaneous phonocardiogram and electrocardiogram, lead II. A summation gallop occurs in mid-diastole; it follows the second heart sound by 0.15 second and the P wave by 0.13 second, and clearly precedes the QRS complex.

DISCUSSION

Over the range of cardiac rates usually encountered the rapid-filling or ventricular gallop sound bears a constant relation to the second heart sound.[1] The mean value for the interval between the second heart sound and the left ventricular gallop (2-vG interval) is 0.15 second. The ventricular gallop in mitral regurgitation is a special case and is not included in the calculation of this mean value.

The left atrial gallop follows the P wave (P-aG interval) by 0.14 second. When cardiac acceleration is sufficient to eliminate the period of slow ventricular filling and cause superposition of the ventricular and atrial gallop sounds, the true summation gallop results. Therefore, the true summation gallop should possess those timing features characteristic of its 2 component gallops. It should follow the second heart sound by 0.15 second and follow the P wave by 0.14 second. It becomes evident that the heart rate at which precise summation occurs is not a matter of chance but is uniquely determined by the different time intervals that comprise a single cardiac cycle.

Figure 6 illustrates a single auscultatory cardiac cycle from one first heart sound to the next. The second heart sound and the summation gallop are also indicated. Above

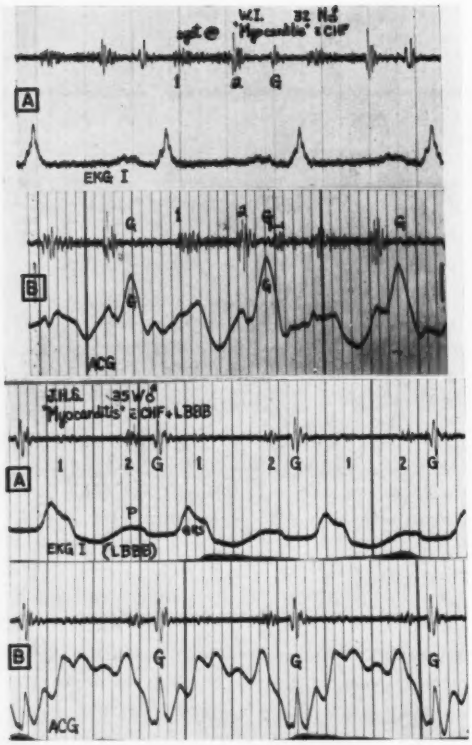

FIG. 4 *Top.* Case 16. *A.* Simultaneous phonocardiogram and electrocardiogram, lead I. The mid-diastolic gallop sound follows the second heart sound by 0.16 second, follows the P wave by 0.13 second, and precedes the QRS complex. *B.* Simultaneous phonocardiogram and apex cardiogram. The gallop sound is best seen in the second cycle shown. The transmitted gallop bulge is large, prominent, and consistently present. The minute heart rate is 107.

FIG. 5 *Bottom.* Case 17. *A.* Simultaneous phonocardiogram and electrocardiogram, lead I. Complete left bundle-branch block is present. The P wave occurs during the end of the T wave with a P-R gallop (*G*) is the loudest of the 3 heart sounds. It interval of 0.20 to 0.22 second. The mid-diastolic follows the second heart sound (*2*) by 0.13 second, follows the P wave by approximately 0.12 second, and precedes the QRS complex. The first heart sound (*1*) is very soft. *B.* Simultaneous phonocardiogram and apex cardiogram. The undulating precordial movement is indicative of severe myocardial disease. Amidst these undulations is a sharp, distinct gallop bulge (*G*) simultaneous with the gallop sound. The gallop bulge produces the most prominent of the precordial movements. The minute heart rate is 102.

the auscultatory cycle is the simultaneous electrocardiogram showing the P wave and the QRS complex. The single cycle is divided into intervals to enable calculation of the cycle duration at which the summation gallop occurs. The duration of this cycle is the sum of its component subdivisions as constructed. We observe from figure 6 that

$$\textit{Summation cycle length (seconds/cycle)} = S+(2\text{-}vG)+(PR)-(P\text{-}aG)+(Q\text{-}1) \qquad (1)$$

This expression is accurate for any given case but is cumbersome for general use. It is simplified by substituting for some of the intervals their numerical mean values. The following values are employed: $S = 0.29$ second. This is the interval between the first and the second heart sounds at a cardiac rate of 109. This rate lies in the middle range of rates at which summation occurs. $(2\text{-}vG) = 0.15$ second. $(P\text{-}aG) = 0.14$ second. These are the most accurate mean values to 2 significant figures for the left heart. The P-aG interval was determined in hypertensive heart disease, which is the most frequent cause of left atrial gallop. It may be a valid mean for other conditions of systolic overload, such as aortic stenosis, but such a statistical study is not available. $(Q\text{-}1) = 0.07$ second. This is the mean value for this interval in hypertensive heart disease.[1, 10]

The P-R interval is left as a variable since its variations are random and occur over a wide range.

On substitution of the above values, equation 1 becomes

$$\textit{Summation cycle length (seconds/cycle)} = (0.29)+(0.15)+PR-(0.14)+(0.07)$$

$$\textit{seconds/cycle} = 0.37 + PR \qquad (2)$$

Taking reciprocals on both sides of equation 2 yields

$$\textit{cycles/second} = \frac{1}{0.37 + PR}$$

Multiplication by 60 gives minute heart rate

$$\textit{cycles/min.} = \frac{60}{0.37 + PR} \qquad (3)$$

Equation 3 provides a useful relation between the heart rate in beats per minute

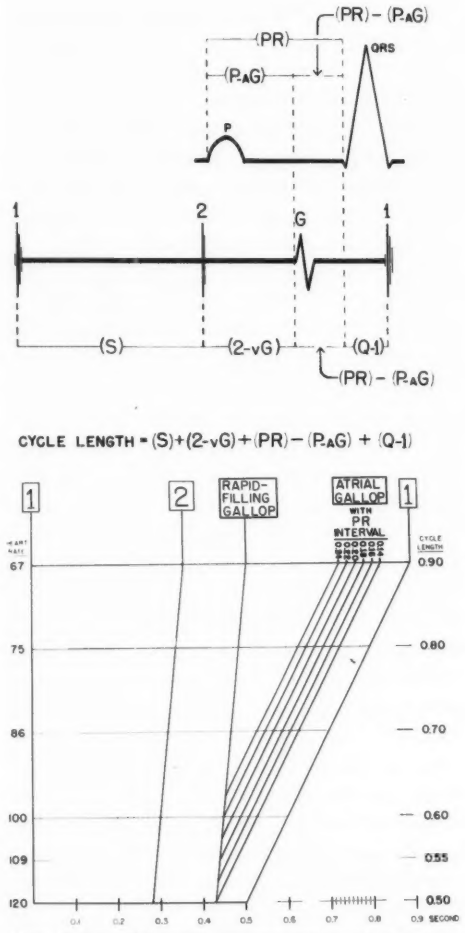

FIG. 6 *Top.* Schematic representation of simultaneous electrocardiogram (*upper tracing*) and phonocardiogram (*lower tracing*) for a single auscultatory cycle in which the summation phenomenon occurs precisely. Then, the gallop sound (*G*) should possess the timing features of both a rapid-filling gallop and an atrial gallop. The single cycle is then divided into intervals to enable calculation of the cycle length in terms of known quantities. The P wave and the QRS complex are labeled as such. *1*, first heart sound; *2*, second heart sound; *G*, summation gallop or augmented gallop; *S*, duration of auscultatory systole; *2-vG*, interval from the second heart sound to the rapid-ventricular-filling gallop; *PR*, electrical P-R (P-Q) interval; *P-aG*, interval from onset of the P wave to the atrial gallop; *Q-1*, interval from onset of the QRS complex to the first heart sound.

FIG. 7 *Bottom.* Graphic representation of a single auscultatory cycle from one first heart sound to the next. Cycle duration in seconds is represented on the vertical axis (*ordinate*) and appears on the right; the corresponding minute heart rate appears on the left. Distance along the horizontal axis (*abscissa*) represents time elapsed from the first heart sound that begins the cycle. The constant relation between the second heart sound and the rapid-filling gallop is represented by respective parallel lines 0.15 second apart. The constant relation between the P wave and the atrial gallop results in a constant interval from the atrial gallop to the ensuing first heart sound for a given P-R interval. The lines representing the time of atrial gallop for a given P-R interval and the ensuing first heart sound are parallel and the distance between them is PR — (PAG) + (Q-1) = PR — 0.14 + 0.07 = PR — 0.07 (in seconds). The intersection of the 2 time lines representing the 2 gallops is the point of precise summation. The ordinate of this point is the summation rate (*left of figure*) or the summation cycle length (*right of figure*).

at which precise summation occurs (i.e., the summation rate) and the P-R interval in seconds. Table 1, column 2, lists corresponding values for the summation cardiac rate and the P-R interval, as calculated from equation 3.

The relation expressed by equations 2 and 3 is depicted graphically in figure 7. This graph was constructed by employing the mean values for the 2-vG, P-aG, and Q-1 intervals. The horizontal width of the figure at any level represents the duration of a single cycle at the corresponding heart rate. The timing of the first, second, rapid-filling gallop, and atrial gallop sounds is indicated by the appropriate straight line. The time of occurrence of the atrial gallop depends upon the timing of the P wave and therefore will vary with the P-R interval. The point of intersection of the time lines representing the rapid-filling and atrial gallops is the point of precise or complete summation. The ordinate or horizontal level of this point gives the cycle duration or the cardiac rate at which summation occurs. The graph illustrates the dependence of the summation cardiac rate upon the P-R interval.

The summation rates for various P-R intervals, determined from the graph, are listed in table 1. At a P-R interval of 0.18 second the summation rate is 109 and is identical with that obtained from equation 3.

TABLE 1.—*Summation Rate as a Function of the P-R Interval*

P-R interval (sec.)	Summation rate, beats per minute, calculated from	
	Equation 3	Graph (fig. 7)
0.14	118	120
0.16	113	114
0.18	109	109
0.20	105	104
0.22	102	100

This precise agreement reflects the substitution in equation 1 of 0.29 second for S, the duration of auscultatory systole at a minute heart rate of 109. The graph of figure 7 takes account of the slight variation of systole with heart rate, and is more accurate to this degree than is equation 2 or 3. Nevertheless, in the range of normal P-R intervals the error of equation 3 resulting from the substitution of a constant value for S is less than 2 per cent.

These calculations may be extended to include the augmented ventricular gallop and the augmented atrial gallop. When ventricular gallop alone is present, cardiac acceleration can superimpose this gallop on the time when atrial gallop would occur (i.e., 0.14 second after the onset of the P wave). The ventricular gallop is then augmented, as evidenced by the marked increase in sound intensity and often by the magnitude of the ventricular bulge. The same is true for an existing atrial gallop superimposed upon the appropriate portion of the rapid-filling period (i.e., 0.15 second after the onset of the second heart sound). Therefore, equations 2 and 3 and the graph are valid for the 2 types of augmented gallop as well as for the true summation gallop.

The fortuitous timing of a premature atrial contraction can momentarily superimpose the phase of atrial contraction upon the period of rapid-ventricular filling and thereby produce the summation phenomenon. When both ventricular and atrial gallops are present, and the premature P wave begins 0.14 second before the ventricular gallop, the 2 gallops are superimposed to produce a summation gallop. If only a ventricular gallop were originally present, the same premature atrial contraction will momentarily augment the existing ventricular gallop. For the abbreviated cycle which is ended by the premature atrial contraction equation 2 is valid and expresses the duration of the shortened cycle in terms of the P-R interval of the premature atrial systole, only if the summation phenomenon has occurred. Conversely, if the values for the P-R interval of the premature atrial systole and the length of the abbreviated cycle satisfy equation 2, then summation certainly has occurred. Reexamination of figure 6 provides a visual aid in understanding summation due to a premature atrial contraction. One must now imagine that the P wave and the QRS complex shown are those of the premature atrial contraction, which has encroached upon the normal diastolic period to produce summation.

Clinical Significance. The true summation gallop and the augmented gallops occur when the heart rate is sufficiently fast. The significance of the true summation gallop is that of its 2 components. The significance of the augmented gallop is that of the single gallop identified when the heart rate is slower. Summation and augmentation only reflect the more rapid heart rate.

SUMMARY

Adequate cardiac acceleration will superimpose the phase of atrial contraction upon the period of rapid ventricular filling. The superposition of these 2 periods is called the summation phenomenon. The cardiac rate at which precise summation occurs and its corresponding cycle length are termed the summation rate and the summation cycle length, respectively.

Both the ventricular gallop and the atrial gallop may be present in each cardiac cycle, producing a quadruple rhythm. When cardiac acceleration is sufficient to produce the summation phenomenon, the 2 gallops are

superimposed to produce the true summation gallop.

When a ventricular or an atrial gallop alone is present the summation phenomenon will augment the intensity of the existing gallop. It is then called augmented ventricular gallop or augmented atrial gallop, respectively.

A single, loud gallop present during tachycardia may be either an augmented gallop or a true summation gallop. The distinction can be made only when the heart rate is slowed, at which time the true summation gallop will change to a quadruple rhythm while the augmented gallop remains a single sound of reduced intensity.

Examples of quadruple rhythm, summation gallop, and augmented gallop are shown.

Two equations were derived that express the summation cycle length or the summation rate, respectively, as a function of the P-R interval. A graphic representation of this relation was also constructed. Of the critical time intervals the P-R interval is the only random variable affecting the summation rate, and its range is the largest.

The equation for the summation cycle length is also valid when the summation is produced by a premature atrial contraction. The cycle in which summation occurs is the shortened cycle, prematurely ended. The duration of such a summation cycle is a function of the P-R interval of the premature atrial contraction, as expressed by the equation derived for the more usual case of summation resulting from cardiac acceleration.

Summario in Interlingua

Adequate acceleration cardiac impone le phase de contraction atrial super le periodo de rapide replenation ventricular. Le superimposition de iste duo periodos es appellate le phenomeno de summation. Le frequentia cardiac al qual un summation precise occurre e le correspondente longor de cyclo es designate, respectivemente, como le frequentia de summation e le longor de cyclo de summation.

Tanto le galopo ventricular como etiam le galopo atrial pote esser presente in un cyclo cardiac individual, con le resultante production de un rhythmo quadruple. Quando le acceleration cardiac es sufficientemente intense pro producer le phenomeno de summation, le duo galopos es superimponite le un al altere con le resultante production del ver galopo de summation.

Quando un galopo ventricular sol o un galopo atrial sol es presente, le phenomeno de summation augmenta le intensitate del galopo existente. Alora illo es appellate un augmentate galopo ventricular o, respectivemente, un augmentate galopo atrial.

Un sol e forte galopo que es presente durante tachycardia pote esser (1) un galopo augmentate o (2) un ver galopo de summation. Le distinction inter le duo pote esser facite solmente post retardar le frequentia cardiac, quando le ver galopo de summation se transforma in un rhythmo quadruple, durante que le galopo augmentate remane un sol sono de intensitate reducite.

Es presentate exemplos de rhythmo quadruple, de galopo de summation, e de galopo augmentate.

Esseva derivate duo equationes que exprime, respectivemente, le longor de cyclo de summation e le frequentia de summation como functiones del intervallo P-R. Un representation graphic de iste relation esseva etiam construite. Inter le critic intervallos de tempore, le intervallo P-R es le sol variabile de hasardo que affice le frequentia de summation, e su gamma de valores possibile es le plus extense.

Le equation pro le longor de cyclo de summation remane valide quando le summation es producite per un prematur contraction atrial. Le cyclo in que le summation occurre es le cyclo abbreviate con termination prematur. Le duration de un tal cyclo de summation es un function del intervallo P-R del contraction atrial prematur, exprimite per le equation que es derivate pro le caso plus usual de summation resultante ab acceleration cardiac.

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Thou, wondrous Harvey, whose Immortal Fame,
By thee instructed, grateful Schools proclaim,
Thou, Albion's Pride, didst first the winding Way,
And circling Life's dark Labyrinth display.
Attentive from the Heart thou didst pursue
The starting Flood, and keep it still in view,
Till thou with Rapture saw'st the Channels bring
The Purple Currents back, and from the Vital Ring

Sir Richard Blackmore, *Creation. A Philosophical Poem Demonstrating the Existence and Providence of a God.* In Seven Books. 8vo. London, 1712. [Blackmore, who went from schoolmaster to physician in ordinary to William III ("His pupils grew blockheads and his patients died.") was violently attacked by Pope, Dryden and Swift, but nothing gagged his muse, and the equally intemperate praise lavished on the "Creation" by Dr. Johnson, Addison and Dennis seemed to justify him.]

Effect of Intravenous Heparin on Human Blood Viscosity

By ARISTIDES GOUSIOS, M.D., AND MARTIN A. SHEARN, M.D.

In view of conflicting reports, the effect of intravenously administered heparin on the viscosity of the blood of normal subjects was evaluated. A simple, in vivo technic based on Poiseuille's law was used in 18 subjects.

SOME investigators[1, 2] have noted a decrease in the viscosity of human blood following the administration of heparin; whereas, others[3] have observed no such change. This discrepancy may be related in part to the methods employed; they entail removal of the blood from the body, and this in itself may lead to alteration of viscosity.

In the present study, the effect of heparin on the viscosity of blood was evaluated in vivo by a technic[4] that does not alter this property.

METHOD

The method of determining blood viscosity employed in the present study is based on Poiseuille's law that during laminar flow of a homogeneous fluid in a tube of constant diameter, the frictional loss bears a linear relationship to the volumetric rate of flow and is independent of the vessel wall. According to Green,[5] blood behaves as a continuous rather than a plastic fluid in vessels greater than 0.4 mm. in diameter. In addition the blood flow in such vessels is laminar[6] unless the Reynolds number exceeds the critical value of 970 ± 80 which is considerably higher than the value obtained in the experimental circumstances of the present study. The viscosity may be determined by passing the blood through a needle of known length and radius while measuring both the rate of flow and the difference between the pressures at the ends of the needle.

The viscosity can then be calculated according to the formula

$$\eta = \frac{f}{q} \cdot \frac{r^4}{8L}$$

where η = viscosity in Gm. second per cm.^{2}, f = frictional loss of energy as cm.^{2} per gram, q = volumetric rate of flow as cm.^{3} per second, r = radius, L = length of needle.

In this formula, since the venous pressure times the density of the fluid in the manometer represents the frictional loss of energy during blood flow in cm.^{2} per gram, and since the density conversion factor of saline is 1, venous pressure in centimeters may be substituted for f. If the second half of the equation is multiplied by the factor 980, grams second per cm.^{2} is converted to dyne second per cm.^{2} or poises; if the result is multiplied by 100, the viscosity is expressed in centipoises, the usual unit of viscosity.

The needles used throughout the study were specially constructed* to have a uniform bore of 0.80 mm. diameter and a length of 70.0 mm. These specifications were chosen in order to satisfy amply both the critical 0.4 mm. diameter and the suggestion of Green[5] that the length of the tube should be at least 20 times its diameter in order to minimize pressure losses that develop as a consequence of the branching system. The needles, recalibrated by determining the flow rate through them of distilled water at 20 C. from a known pressure head, were found to be identical.

The technic, which is essentially like that described by Pirofsky[4] with slight modifications, was standardized as follows. A blood pressure cuff was applied about 6 cm. above the elbow of the subject and inflated to between 20 and 22 mm. Hg. This allowed for a venous pressure of approximately 270 to 300 mm. of saline solution, thus insuring an adequate flow rate. The pressure cuff did not influence blood viscosity, as proved by repeated measurements on the same subject with and without the cuff. This suggests a linear relationship between pressure and flow rate at least within the narrow pressure range herein studied, which is in keeping with the observations of Bayliss.[7] A vein of adequate size within the antecubital area was selected and the site was infiltrated with 2 per cent procaine to avert discomfort and restlessness of the subject during the procedure. The calibrated needle was inserted with the bevel upward, and the venous pressure was determined by means of a saline solution manometer with a 3-way stopcock. When the venous pressure was stable, the stopcock and manometer were removed, and the

From the Kaiser Foundation Hospital, Oakland, Calif.

*Courtesy of Becton, Dickinson and Company, Rutherford, N. J.

TABLE 1.—*Viscosity in Centipoises Before and After Intravenous Heparin*

Patient	Control	Mean	Viscosity 15 min. following 80 mg. heparin	Mean	Change
A.F.	3.33		3.17		
	3.24	3.25	3.18	3.18	—.07
	3.19		3.18		
S.B.	3.19		2.96		
	3.28	3.32	3.13	3.10	—.22
	3.48		3.20		
J.Y.	2.79		2.68		
	2.73	2.75	2.75	2.73	—.02
	2.72		2.75		
A.G.	3.18		3.12		
	3.18	3.18	3.24	3.17	—.01
	3.17		3.16		
B.D.	2.31		2.26		
	2.25	2.25	2.25	2.26	+.01
	2.19		2.26		
H.A.	2.38		2.50		
	2.36	2.37	2.30	2.40	—.03
B.A.	2.87		2.88		
	2.85	2.85	2.89	2.88	+.03
	2.83		2.88		
A.A.	3.18		3.12		
	3.18	3.22	3.24	3.17	—.05
	3.30		3.16		
S.S.	2.50		2.48		
	2.59	2.56	2.52	2.49	—.07
	2.60		2.48		
B.D.	2.41		2.35		
	2.37	2.42	2.34	2.37	—.05
	2.48		2.44		

blood flowing freely through the needle was collected directly into a calibrated tube for a period of 30 seconds, timed by a stop-watch. The venous pressure was then immediately rechecked. It was almost always found to be unchanged; if a variation of 3 mm. of saline solution had occurred, the sample was discarded. Replicate samples, usually 3, were collected in this manner from each subject and the viscosity of each sample was determined by substituting in the formula milliliters of blood per second for q and the venous pressure for f.

The residual standard deviation as determined by a two-way analysis of variance on the data of tables 1 and 2 was 0.065 centipoise yielding a coefficient of variation of 2.2 per cent. In terms of least significant difference a deviation of 0.135 centipoise between determinations based on the mean of 3 measurements before and 3 measurements after heparin is significant at the 1 per cent level of significance. More than 200 separate determinations have now been carried out by this method, which we found simple and easily reproducible.

Eighteen experiments were performed on 15 subjects in the fasting state, 1 subject (B.D.) being studied on 4 occasions. In no subject was there a clinically evident abnormality of blood coagulation or of lipid metabolism. After replicate determinations of blood viscosity had been performed on each subject, 80 mg. of heparin were injected intravenously. In 10 instances the viscosity was again determined at the expiration of 15 minutes, and in 8 instances at the expiration of 45 minutes. In each experiment, the hematocrit level was determined by the Wintrobe method; in no instance was there variation greater than 1 per cent. The clotting time of the blood before and after the administration of heparin was determined by the method of Lee and White to test the potency of the batch of heparin employed.

RESULTS

Results are recorded in tables 1 and 2. The greatest individual decrease of viscosity following heparin administration was 0.22 centipoise; the greatest increase was 0.20 centipoise. The mean change in viscosity 15 minutes after heparin administration was −0.04 centipoise; 45 minutes after heparin administration the mean change was −0.05 centipoise. This small decrease represents a change of only 1.6 per cent. Although this is significant statistically, it would appear to have no importance from either a clinical or physiologic standpoint. For comparison, the change in viscosity that occurs with a 1 per cent alteration in hematocrit in normal subjects is of greater magnitude[4] than the mean change recorded in the subjects of the present study after heparin.

DISCUSSION

Viscosity is that property of a fluid which results in resistance to flow; it is related to the internal frictional characteristics of the fluid. The measurement of blood viscosity is an important factor in any hemodynamic consideration. Clinically, it derives special interest from the relationship of this property to intravascular thrombosis.

TABLE 2.—*Viscosity in Centipoises Before and After Intravenous Heparin*

Patient	Control	Mean	Viscosity 45 min. following 80 mg. heparin	Mean	Change
B.D.	2.36		2.32		
	2.30	2.35	2.26	2.29	—.06
	2.40		2.28		
S.G.	3.64		3.85		
	3.74	3.63	3.81	3.83	+.20
	3.52		3.81		
H.G.	3.64		3.54		
	3.72	3.68	3.67	3.58	—.10
			3.54		
W.G.	3.54		3.44		
	3.54	3.57	3.44	3.40	—.17
	3.62		3.32		
P.P.	3.83		3.66		
	3.83	3.85	3.80	3.75	—.10
	3.88		3.80		
S.P.	3.13		3.22		
	3.01	3.13	3.13	3.15	+.02
	3.26		3.10		
B.D.	2.51		2.43		
	2.46	2.47	2.35	2.37	—.10
	2.45		2.33		
D.J.	3.44		3.32		
	3.44	3.44	3.32	3.32	—.12

The viscosity of blood depends to a large degree upon the size and concentration of the particles in suspension, principally the red blood cells. The many factors that influence it have been summarized by Pirofsky;[4] among them are the concentration of proteins, temperature, degree of sedimentation, and carbon dioxide content.

During the process of coagulation, the viscosity of blood increases.[8] Under these circumstances, heparin, by virtue of its anticoagulant properties, would be expected to decrease blood viscosity to its previous level. The very small decrease in viscosity noted in the present study may well have been an effect of anticoagulation rather than a real effect of heparin on viscosity.

Viscosity may increase in hyperlipemic states;[9] heparin might therefore be expected to reduce viscosity, since it participates in the clearing of chylomicrons from serum.[10] All of the subjects here studied were fasting and none had hyperlipemia; hence no appreciable effect of heparin on their lipid levels could be expected.

Removal of the blood from the body may result in cooling, sedimentation, clotting—factors that in themselves alter viscosity. These major disadvantages of viscosity determinations by means of in vitro viscometers are obviated by the use of the simple in vivo technic here employed. The method requires no expensive equipment and its reproducibility compares favorably with that of other methods.

SUMMARY

The effect of heparin on the viscosity of blood was studied by means of a simple, reproducible, in vivo method based on Poiseuille's law. The data indicate that heparin causes a fall of very small magnitude of the viscosity of human blood, which is probably of no clinical or physiologic importance.

SUMMARIO IN INTERLINGUA

Le effecto de heparina super le viscositate del sanguine esseva studiate in vivo per medio de un simple e reproducibile methodo que es basate super le lege de Poiseuille. Le datos indica que heparina causa un reduction del viscositate del sanguine human sed que iste reduction es si micre que illo ha probabilemente nulle signification clinic o physiologic.

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The various organs, the diseases of which are subdivided for treatment, are not isolated, but complex parts of a complex whole, and every day's experience brings home the truth of the saying, 'When one member suffers all the members suffer with it.' Plato must have discussed this very question with his bright friends in the profession—Eryximachus, perhaps—or he never could have put the following words in the mouth of Socrates:—

> 'I dare say that you may have heard eminent physicians say to a patient who comes to them with bad eyes, that they cannot cure the eyes by themselves, but that if his eyes are to be cured, his head must be treated: and then again they say that to think of curing the head alone and not the rest of the body also, is the height of folly. And arguing in this way they apply their methods to the whole body, and try to treat and heal the whole and the part together. Did you ever observe that this is what they say?'—WILLIAM OSLER, M.D. *Remarks on Specialism*. Boston Med. & Surg. Journal, 1892.

Electrocardiographic Studies in Pulmonary Disease

I. Electrocardiographic Abnormalities in Diffuse Lung Disease

By David H. Spodick, M.D.

Electrocardiograms of 79 consecutively admitted patients with diffuse lung diseases were analyzed. The frontal plane P-wave axis and the P-wave configuration in limb and precordial leads emerged as the common denominator for the large majority of the group. Other abnormalities were common but not so characteristic.

IN MANY respects the lungs and heart comprise a functional unit with interrelations such that disease of one may often affect the other. The electrocardiogram bears a unique relationship to this situation, not only because it reflects certain aspects of cardiac function but also because much of the cardiac potential must traverse lung tissue to reach the recording electrodes.

The observations in these studies suggest a marked, and relatively specific, effect of diffuse lung disease upon both normal and abnormal electrocardiograms.

Material and Methods

Electrocardiograms were analyzed in 79 consecutive hospital admissions (ages 32 to 84) for diffuse lung disease. Almost all of these patients had emphysema, in the majority associated with chronic bronchitis, bronchiectasis, or pulmonary fibrosis. This investigation revealed certain common characteristics in highly significant percentages of these tracings. Many of the results resembled the findings of Zuckermann[1] and of Sodi-Pallares,[2] but differed in detail.

Conventions adopted for this report are as follows: 1. The standard hexaxial modification of the Bayley reference system is used for plotting the derived frontal plane axes. 2. The designation "Â" denotes mean manifest axis, e.g., Â P = +90° or Â QRS = +90° respectively indicate frontal mean P wave or QRS axis perpendicular to lead I and equally positive in leads II and III.

Results

The following elements of the electrocardiogram were most influenced by the presence of diffuse lung disease: mean frontal P-wave Axis (Â P), P-wave configuration in frontal-plane leads; P-wave configuration in right precordial leads, mean frontal QRS Axis (Â QRS). ST-T complex abnormalities were noted in the over-all electrocardiographic evaluation but were excluded from study in relation to lung disease because of the use of digitalis in some patients.

Mean Frontal Â P

In most normal adults, the mean manifest frontal P axis is generally considered to vary within a narrow zone, +45° to +64°.[1-3] The most constant finding in patients with diffuse lung disease is the relatively rightward (vertical) tendency of this vector. Table 1 indicates its orientation in 71 consecutive cases with sinus rhythm.* The overwhelming majority (83 per cent) were clearly vertical.

Because only 12 instances (17 per cent) were to the left of +70°, these cases were further analyzed to determine whether there were common factors causing them to differ from the majority. Pulmonary lesions in these patients were quite typical of the entire series. Seven cases with Â P = 60° (i.e., P wave flat or diphasic in aV_L) were considered intermediate or "borderline." Five of these had marked verticality of the QRS axis although 4 had conditions associated with left heart strain. Similarly, of the 5 cases with "leftward" P axes (+50° – +30°), 4 had systemic hypertension, yet 3 had QRS axes of +70° to +90°.

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*There were 3 cases each of atrial fibrillation and atrioventricular nodal rhythm, and 2 with flat P waves in the limb leads, in the total 79.

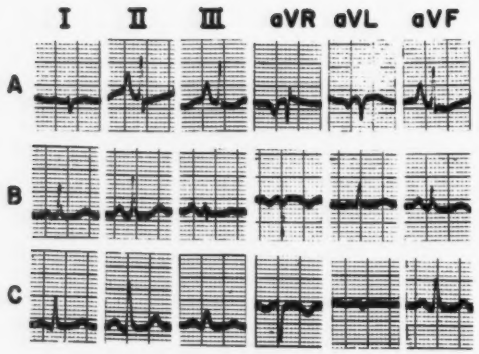

FIG. 1. P-wave configuration in limb leads of patients with lung disease. *A*, P pulmonale; *B*, Gothic P wave; *C*, cupola (normal appearing) P wave.

P-Wave Configuration in Frontal Plane Leads

Three types of P-wave configuration were present: 1. Classical P-pulmonale of Winternitz[4] (fig. 1*A*). 2. "Gothic" P of Zuckerman[1] —definite single peaking of a P of normal dimensions in leads II, III, and aV_F (fig. 1*B*). 3. Normal-appearing, cupola-shaped P wave (fig. 1*C*). P-pulmonale and Gothic type P waves occurred only with $\hat{A}$ P = +70° or greater. Cupola P waves were found with any axis. The occurrence of these P types is listed in table 2, from which it is evident that over half of all cases (55 per cent) had either P pulmonale or Gothic P waves. Of the 59 cases with $\hat{A}$ P = +70° to +90°, 30 (51 per cent) had Gothic P waves and 39 (66 per cent) had either Gothic or pulmonale P types.

P-Wave Configuration in Right Precordial Leads

Of 73 cases in sinus rhythm,* 37 (51 per cent) showed diphasic (+ −) P waves in at least V_1 and V_2, and in some as far as V_4 (fig. 2). Twenty-nine (78 per cent) of these were associated with $\hat{A}$ P = +70° to +90°.

Mean Frontal Â QRS

While the most consistent effect of lung disease was on the atrial complexes, verticality of frontal $\hat{A}$ QRS was seen in about one half of these patients (table 3). Almost one half (44 per cent) of the patients had an unmistakable vertical $\hat{A}$ QRS (+70° or more), which is quite uncommon for these age groups. This figure is more impressive if to it is added those with $\hat{A}$ QRS = −80° to −90° and those with "indeterminate" frontal $\hat{A}$ QRS, the total thus becoming 57 per cent. These groups represent a special situation, which may be designated the "axis-illusion" phenomenon.

Axis-Illusion Phenomenon of Â QRS. Littmann[6] has pointed out that if the apical portion of the heart is rotated posteriorly (in an electrical sense), its arc would eventually carry it above the "horizon" as viewed anteriorly. An axis of −80° or −90° is quite unusual in the absence of infarction of the

*The 2 cases with flat P waves in the limb leads had clear precordial P waves.

TABLE 1.—*Orientation of Frontal Â P in Seventy-One Patients with Diffuse Lung Disease*

Â P	No. of cases	%
+90° to +70°	59	83
+60°	7	10
+50° to +30°	5	7

TABLE 2.—*P-Wave Configuration in Seventy-One Cases of Diffuse Lung Disease with Sinus Rhythm and Measurable Frontal P Waves*

P type	Â P = +70° to + 90°	Â P = +60° to +30°	% of 71 cases
Pulmonale	9	0	13
Gothic	30	0	42
Cupola	20	12	45
Totals	59	12	100

TABLE 3.—*Orientation of Â QRS in Seventy-Nine Patients with Diffuse Lung Disease*

Â QRS	Number of cases	Per cent
+120° to +70°	35	44
+ 70° to +30°	22	28
+ 20° to −60°*	12	15
−80° to −90°	7	9
Indeterminate	3	4
Totals	79	100

*There were no cases with Â QRS = −70°.

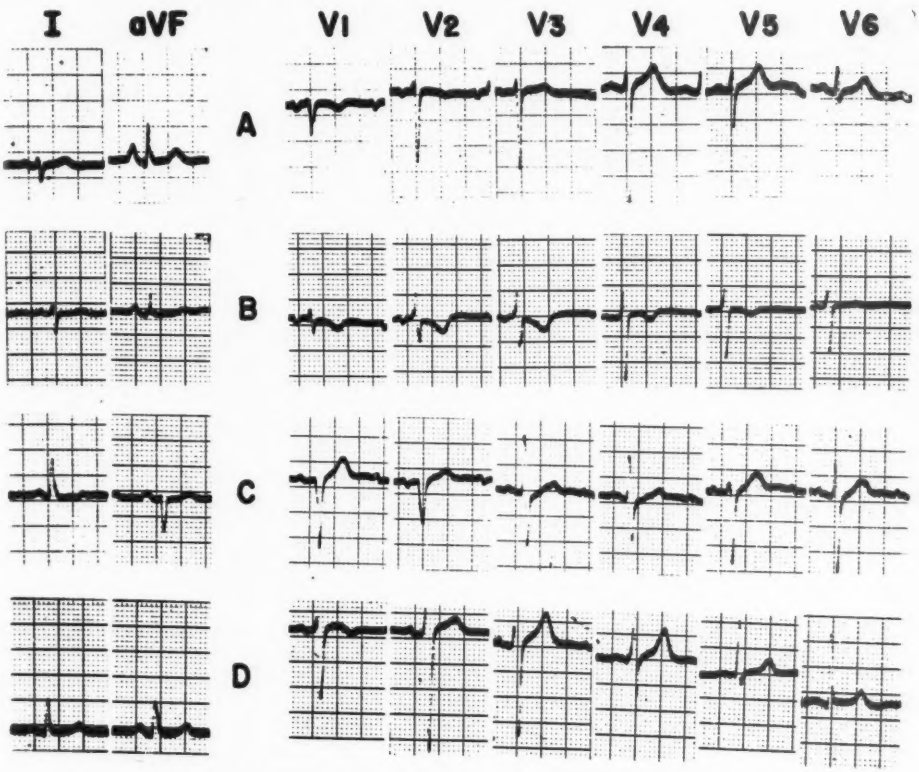

FIG. 2. P-wave configuration in precordial leads of patients with lung disease. Clearly diphasic (+ —) P waves are seen at least to V_2 and as far as V_4 (*B*). *A*, with P pulmonale; *B*, with gothic P wave; *C*, with cupola P wave and "horizontal" QRS axis; *D*, with cupola P wave and "intermediate" QRS axis.

diaphragmatic aspect of the left ventricle. It was interesting to find 7 such axes in the lung disease group. None of these patients had evidence or history suggesting myocardial infarction and none had known left ventricular disease. Six of them had deep S waves in all precordial leads and the seventh had incomplete right bundle-branch block with rSr′ in V_1 and rS in aV_F. The 2 designated "indeterminate frontal Â QRS" were so labeled because R was equal to q + S in all extremity leads: both of these had deep S waves from V_1 to V_6. Thus, in all 9 cases Â QRS was directed quite posteriorly. If this situation is visualized in the sagittal plane, it is clear to see why a −80° or −90° axis or an indeterminate frontal (i.e., directly posterior) axis may not be very different from an axis of +80° or +90°. Figure 3 demonstrates that the frontal projection of a posteriorly directed Â QRS may be either +90° or −90° due to very small differences in its sagittal plane angle. The large frontal plane discrepancy (180°) is thus an illusion due to small deviations from the sagittal "horizon" of mean vectors which are actually quite close to each other in space.

Horizontal Axes

The 12 cases of diffuse lung disease with a relatively leftward QRS axis (+20° to −60°) formed 15 per cent of the group. These were analyzed in the same manner as those with a relatively leftward P axis. Of 9 of these

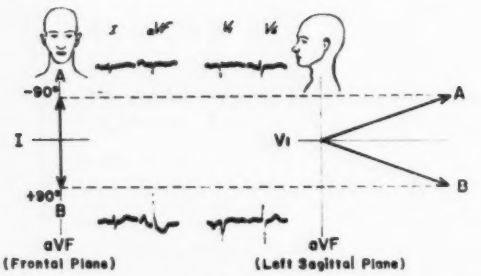

FIG. 3. The *axis-illusion* phenomenon. *A* and *B* are frontal mean QRS axes of −90° and +90° respectively, suggesting a 180° divergence. Their sagittal projections reveal that this is illusory, since they are actually much closer in space.

cases with measurable P vectors,* 5 had Â P = +90° and there were 1 each with Â P of +70° and +80°. Furthermore, half of these patients had evidence of left-sided heart disease. One of the others had a congenital chest deformity. As with the P vector, most cases with leftward deviation of Â QRS can be accounted for by disease of the left side of the heart and systemic circulation. Despite this, the majority of these continue to show a vertically oriented Â P.

Precordial QRS Configuration

The tendency to posterior orientation of Â QRS was well shown in the precordial leads. In 51 cases (65 per cent)there was an S wave of 2 mm. or more to position V_5 or V_6 (to V_6 in all but 2). In many, rS or RS complexes occurred in all precordial leads. The presence or absence of this configuration had a close relation to the orientation of frontal Â QRS and Â P. This is shown in table 4, from which it is clear that there was a high degree of correlation with verticality of frontal Â QRS, 38 cases (75 per cent) having an axis of over +70°, −80° to −90°, or "indeterminate." More remarkable was the striking correlation with the frontal P axis: of 46 cases with measurable frontal Â P, 41 (89 per cent) had Â P of +70° to +90°.

*Three cases were not measurable because of atrial fibrillation, nodal rhythm, and flattened P waves.

TABLE 4.—*Relation of Precordial QRS Configuration to Mean Frontal Â QRS and Â P*

Â QRS	Number of cases: S to V_5 or V_6 = 2mm. or more	Number of cases: S absent or under 2 mm., to V_5 and V_6
+70° to +120°	30	6
+30° to + 60°	7	13
+20° to −60°	6	7
−80° to −90°	6	2
Indeterminate	2	0
Totals	51	28
Â P		
+70° to +90°	41	17
+60°	3	5
+30° to +50°	2	3
Totals	46*	25†

*The other 5 patients had nodal rhythm or atrial fibrillation.

†The other 3 patients had flat P waves (2) and nodal rhythm (1).

Additional Observations

Thirty-six tracings were entirely within normal limits by standard criteria, excepting for P or QRS axes and configurations consistent with lung disease. There were but 7 cases of unequivocal right ventricular hypertrophy (Goldberger's criteria[5]). Of 8 cases with the electrocardiographic diagnosis of left ventricular hypertrophy, each had leftward deviation of either Â P or Â QRS, despite which 3 had Â P = +80° or +90° and 2 others had Â QRS = +70° and +90° respectively. Of 5 patients with incomplete right bundle-branch block (rSr′ in V_1) and 2 with complete right bundle-branch block, 6 had Â P = +80° or + 90° and 1 had atrial fibrillation. A single patient had left bundle-branch block (but with an Â P of +90°). Twenty-seven patients had a depression of the P-R interval in II, III, and aV_F consistent with atrial T wave: 14 of these had Gothic and 4 others pulmonale-type P waves.

DISCUSSION

Verticalization of the QRS axis by lung disease has long been appreciated. Zuckermann[1] and Sodi-Pallares[2] first called attention to the rightward tendency of the P vector. The present study emphasizes that P

rticality is the predominant and single enrely distinctive finding. Only 44 per cent the patients had Â QRS to the right of 60°; addition of the "*axis illusion*" groups ises this to just over one half (57 per cent). y contrast, the frontal P axis was +70° or ore in fully 83 per cent, making this findg far more characteristic.

The specificity of P verticality relative to ther conditions associated with right heart train is suggested by comparison with the findngs in patients with mitral stenosis and atrial ptal defect. Electrocardiograms in 106 ases of mitral stenosis were reviewed; 40 of hese were in sinus rhythm. The data on 90 atients with atrial septal defect in sinus hythm reported by Toscano-Barboza and olleagues[7] were converted to percentages. These groups are compared with the patients with lung disease in table 5. The enormous preponderance of vertical Â P in the lung disease group is well shown. It is of interest that of the 6 mitral patients who had vertical Â P, 3 had extensive pulmonary disease. Furthermore, 5 of the 6 had distinctive mitral P waves.

TABLE 5.—*Comparison of Mean Frontal P Axis (Â P) in Seventy-one Patients with Lung Disease, Forty with Mitral Stenosis and Ninety with Atrial Septal Defect*

	Â P (per cent)			
	+90° to +70°	+60°	+50° to +30°	+20° to −10°
Lung disease	83	10	7	0
Mitral stenosis	15	20	48	18
Atrial septal defect	27	16	47	11

SUMMARY

The results of this study indicate that the following statements may be made with regard to the electrocardiogram in patients with diffuse lung disease: 1. The chief single electrocardiographic finding in diffuse lung disease is verticalization of the mean frontal P axis. An axis of +70° to +90° is most characteristic. 2. A frontal Â P of +50° or less in such patients is almost always associated with additional disease causing left-sided heart strain (i.e., arteriosclerotic or hypertensive heart disease). 3. Frontal Â P = +60° is a borderline finding in these patients. 4. Distinct single-peaking (either "Gothic" or "pulmonale") of frontal plane P waves is a characteristic occurrence but may be absent. 5. Diphasic (+−) P waves in several right precordial leads occur in about one half of the cases and are more likely to be present when frontal P waves are of Gothic or pulmonale types. 6. A vertical frontal QRS axis occurs in almost 60 per cent of cases if those cases displaying the axis-illusion phenomenon are added to those with Â QRS = +70° or more. 7. Leftward Â QRS (+20° to −60°) in these patients, like "leftward" Â P, is almost always associated with demonstrable conditions causing left heart strain. 8. Deep S waves over the left precordium (i.e., posterior spatial QRS orientation) occur in the majority of patients and correlate well with vertical Â QRS (75 per cent), but much better with vertical Â P (89 per cent).

It is clear that the P wave is the key to the electrocardiographic inference of diffuse lung disease. Rightward mean frontal P axis is its most constant single characteristic. Other factors occur in most cases and may be considered "typical" but are frequently absent. Among these are Gothic and pulmonale-type P waves, vertical Â QRS, deep S waves over the left precordium, and prominent diphasic P waves over the right precordium. Absence of rightward frontal Â P is strongly against the presence of diffuse lung disease. Absence of any other single factor is of little statistical value in itself.

ACKNOWLEDGMENT

The author wishes to acknowledge the technical assistance of Constance A. Dorr, B.M.

SUMMARIO IN INTERLINGUA

Le resultatos de iste studio indica que le sequente assertiones pote esser facite con respecto al electrocardiogramma de patientes

con diffuse morbo pulmonar: (1) Le principal constatation electrocardiographic individual in diffuse morbo pulmonar es verticalisation del axe P frontal medie. Un axe de inter +70 e +90 grados es multo characteristic. (2) Un Â P frontal de +50 grados o minus in tal patientes es quasi semper associate con un morbo additional que es responsabile pro le imposition de un effortio super le corde sinistre (i.e. morbo cardiac arteriosclerotic o hypertensive). (3) Un Â P frontal de +60 grados es un constatation limite in iste patients. (4) Distincte culmines singular del typo gothic o pulmonal in le undas P del plano frontal es un occurrentia characteristic, sed illo pote esser absente. (5) Undas P diphasic (+ −) in plure derivationes dextero-precordial occurre in circa un medietate del casos e es plus probabile quando le undas P frontal es del typo gothic o pulmonal. (6) Un vertical axe QRS frontal occurre in circa 60 pro cento del casos si le casos con le phenomeno del axe illusori es addite al casos con Â QRS de +70 grados o plus. (7) Un Â QRS sinistrorse (+20 a −60 grados) in iste patientes, precisemente como un Â P sinistrorse, es quasi semper associate con le present ia demonstrabile de conditiones que causa le imposition de un effortio super le corde sinistre. (8) Profunde undas S supra le precordio sinistre (i.e. un orientation posterior de QRS spatial) occurre in le majoritate del patientes e exhibi un bon grado de correlation con vertical Â QRS (75 pro cento) sed un correlation ancora multo melior con vertical Â P (89 pro cento).

Il es clar que le unda P es le clave al inferentia electrocardiographic del presentia de diffuse morbo pulmonar. Un dextrorse axe P frontal medie es su plus constante characteristica individual. Altere factores occurre in le majoritate del casos e pote esser considerate como typic, sed il occurre frequentemente que illos es absente. Istos include undas P del typos gothic e pulmonal, vertical Â QRS, profunde undas S supra le precordio sinistre, e prominente diphasic undas P supra le precordio dextere. Le absentia de un dextrorse Â P frontal argue fortemente contra le presentia de diffuse morbo pulmonar. Le absentia de un altere factor individual es de paue valor statistic per se.

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Electrocardiographic Studies in Pulmonary Disease

II. Establishment of Criteria for the Electrocardiographic Inference of Diffuse Lung Disease

By David H. Spodick, M.D.

Criteria based on changes in P waves are proposed for the electrocardiographic detection of diffuse lung disease. In a "blind" evaluation of 100 consecutively admitted patients these proved highly accurate.

THE results of analysis of the electrocardiographic records in part I of these studies suggested that it might be possible to infer the presence of diffuse lung disease from the electrocardiogram alone with considerable accuracy. It is apparent that the significance and applicability of such a procedure would be enhanced if a minimum of criteria were necessary. Accordingly, a deliberately simple basis was adopted: the axis of the frontal plane P waves.

The following criteria were chosen for a positive or possible inference of pulmonary disease; all tracings lacking any of these were considered to be negative for this inference.

Positive Diagnosis ("Consistent with Diffuse Lung Disease")

Any of the following were considered diagnostic, regardless of other abnormalities on the tracings: 1. Presence of P pulmonale or unmistakable "Gothic" P in II, III, and aV_F. 2. Frontal $\hat{A}$ P = + 70° or more and + − P waves to V_2 or beyond, or, precordial S wave of 2 mm. or more to V_6 (or both). 3. Frontal $\hat{A}$ P = + 60° and all 3 of the following: Vertical or "axis illusion" $\hat{A}$ QRS, precordial S wave of 2 mm. or more to V_6, and prominent + − P waves to or beyond V_2.

Possible Diagnosis

Any of the following were considered suggestive, but not conclusive evidence of pulmonary disease. 1. Frontal $\hat{A}$ P = + 60° and any 2 of the following: vertical or "axis-illusion" $\hat{A}$ QRS, precordial S wave of 2 mm. or more to V_6, or prominent + − P waves to or beyond V_2. 2. Frontal $\hat{A}$ P = + 30° to + 50° and all 3 of the above. 3. Frontal $\hat{A}$ P = + 70° or more with frontal $\hat{A}$ QRS = + 70° or more.

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Evaluation of Criteria

One hundred consecutively admitted patients who were free of cardiac arrhythmias were studied. Electrocardiograms of these patients were analyzed without any other knowledge of the patient; even the patient's name was omitted. Tracings were interpreted as: "consistent with diffuse lung disease," "possibly consistent with diffuse lung disease," and "no evidence of diffuse lung disease." These interpretations were then correlated with chest x-rays, physical examination and, in some cases, autopsy and surgical data. A positive chest x-ray or positive pathologic examination was considered a *sine qua non* (table 1). (The interpretation "possibly consistent with diffuse lung disease" is considered to be correct when lung disease was actually present.)

From these figures it is evident that the criteria in themselves were highly accurate in this group of patients with regard to defi-

Table 1.—*Electrocardiographic Analysis for Evidence of Diffuse Lung Disease in 100 Consecutive Adult Patients*

Electrocardiographic interpretation	Total patients	Correct	Incorrect	Per cent correct
Consistent with diffuse lung disease	14	13	1	93
Possibly consistent with diffuse lung disease	10	6	4	60
No evidence of diffuse lung disease	76	73	3	96
Totals	100	92	8	

TABLE 2.—*Analysis of Errors*

No.	Incorrect diagnosis	Â P	Â QRS	Precordial leads	Clinical data
1.	"Positive"	+70°	0°	+ — P to V_3	Hypertension, left ventricular hypertrophy, pulmonary edema
2.	"Negative"	+60°	— 10°	S to V_6	Emphysema. Hypertension (180/110), left ventricular hypertrophy
3.	"Negative"	+60°	+50°		Emphysema. Hypertension (236/110), left ventricular hypertrophy
4.	"Negative"	+60°	+ 30°		Pulmonary adenocarcinoma, emphysema. Mediastinal shift to right
5.	"Possible"	+60°	+100°	+ — P to V_2	Emphysema
6.	"Possible"	+60°	Indeterminate	S to V_6	Aberrant right colon between liver and diaphragm
7.	"Possible"	+60°	Indeterminate	S to V_6	Left ventricular hypertrophy; bilateral pleural effusion
8.	"Possible"	+80°	+ 80°		Hypertensive heart disease

nite diagnosis or exclusion of lung disease. The over-all error for the criteria per se was only 8 per cent (8 of 100 incorrect). However, this appears somewhat optimistic when the influence of the 10 cases in the "possible" group is taken into account.

If only the positively diagnostic criteria were employed, the cases in the "possible" group would have to be shifted to the "negative" group. Under these conditions 77 of a total of 86 cases without diffuse lung lesions (90 per cent) would have been correctly excluded. However, 6 patients of a total of 22 with diffuse lung disease would have been missed. If, conversely, the "possible" cases were induced with the "positive" group (which is more logical), 19 of 22 cases with diffuse lung disease would have been correctly identified—a positive accuracy of 86 per cent; only 5 patients of 78 without lung disease (6 per cent) would have been falsely labeled.

Analysis of Errors

Some light may be cast on the validity of these criteria by an analysis of those cases which were misinterpreted (table 2).

From these data, the following facts are especially noteworthy: 1. Two of the 3 "false negatives" had hypertensive disease and the third had a mediastinal shift. 2. One (no. 7) of the 4 cases which did not have diffuse lung disease, but were considered "possible," had bilateral pleural effusion and another (no. 6) had upward displacement of the right diaphragm by an aberrant loop of colon. 3. Six of the 8 cases had Â P = + 60°, again emphasizing the conclusion drawn in part I of these studies—this P axis, in itself, is a "borderline" finding.

Summary

The following statements may be made with regard to the criteria described for the electrocardiographic inference of diffuse lung disease: 1. Frontal P wave axis and configuration are effective bases for this interpretation. 2. The criteria described appear to be highly accurate in positively identifying (93 per cent) or excluding (96 per cent) cases of diffuse lung disease with the exception of a small "possible" group (10 per cent of patients in this series) in whom the accuracy was only 60 per cent. Nevertheless, if the "possible" group is included with the "positive" group, fully 86 per cent of cases were correctly diagnosed and only 6 per cent of cases without lung lesions were falsely labeled. 3. Some of the errors of diagnosis were associated with the presence of other diseases and mechanical abnormalities of the chest. (This matched the findings in the atypical cases in part I of these studies.) 4. It is proposed that the criteria employed in this study are adequate for a new standard electrocardiographic interpretation: "consistent with diffuse lung disease."

Hypocholesteremic Effect of Benzmalacene

By Irvine H. Page, M.D., and Roland E. Schneckloth, M.D.

A new substance, Benzmalacene, was tested to determine whether it had hypocholesteremic effect in normotensive, hypertensive and hypercholesteremic patients. It proved effective. But after 4 months' treatment liver function began to deteriorate. It is strongly urged that drugs which interfere with cholesterol synthesis in the body be studied most carefully for long periods before widespread clinical trials to prevent atherosclerosis are attempted.

ONE approach to the problem of prevention of atherosclerosis is the prevention of hyperlipemia and, more specifically, hypercholesteremia. Diet, nicotinic acid, and β-sitosterol have been most commonly used for this purpose, and with some success, in reducing hyperlipemia. Recently, attempts have been made to suppress the synthesis of cholesterol in the hope that hypercholesteremia would be abolished and yet leave hormonal syntheses and other metabolic functions of steroids undisturbed. Feeding of delta-4-cholestenone suppressed hepatic cholesterol synthesis and reduced the serum cholesterol level, but caused marked adrenal hypertrophy as well.[1] A number of other agents have been tried with limited success and these have been well reviewed by Kritchevsky[2] and by Curran and Azarnoff.[3]

It has been shown that probenecid inhibits acetate activation of coenzyme A as the latter is involved in glycine conjugation with p-aminobenzoic acid.[4] Recently a compound has been synthesized that is 10 times more active than probenecid in its ability to inhibit renal tubular secretion of penicillin. Correspondingly, it is more active in inhibiting incorporation of acetate and mevalonic acid into the synthesis of cholesterol in vitro.[5]

This substance, Benzmalacene,* is a derivative of the monamide of maleic acid, having an aralkyl group on the nitrogen. Its structure (fig. 1) is quite different from probenecid and carinamide though its actions seem similar. It is believed to be well absorbed by the gastrointestinal tract in the form of the sodium salt.

The work of Beyer and his associates[4] made it seem reasonable that Benzmalacene might be useful in reducing hypercholesteremia in man. Plasma cholesterol levels in dogs were sharply reduced by daily doses of 50 to 300 mg./Kg. and the production of hypercholesteremia in rats and chickens was inhibited.[5]

On the basis of these results we have studied Benzmalacene to determine its effects on the serum cholesterol levels in 6 women and 13 men. Of the 19 patients, 10 had severe essential hypertension and 2 presented the syndrome of malignant hypertension: 7 other patients exhibited hypercholesteremia or hyperlipemia. All hypertensive patients were on free diets at home except for moderate salt restriction. Five of the 7 patients with abnormal serum lipid patterns had followed a carefully controlled diet, containing 50 to 80 Gm. of fat as vegetable oil, for periods ranging from 6 to 18 months; the remaining 2 patients (cases 16 and 17) had eaten freely chosen foods.

The dose of Benzmalacene was 250 mg. given by mouth 2 to 4 times daily after meals; the average daily dose was 750 mg.

Results

Administration of Benzmalacene to Hypertensive Patients. All but 2 (cases 8 and 12) of the 12 hypertensive patients showed a fall

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*[N-(1-methyl-2,3-di-p-chlorophenylpropyl-maleamic acid)], kindly supplied by Dr. Karl Beyer and Dr. E. W. J. De Maar of Merck Sharp and Dohme, West Point, Pa.

TABLE 1.—*Change in Serum Cholesterol in Hypertensive Patients after Administration of Benzmalacene*

Patients (case no.)	Serum cholesterol (mg. per cent)									Weight change (lbs.)
	Mean control cholesterol	1 month	Change	2 months	Change	3 months	Change	4 months	Change	
1	223	165	— 58	183	—40	159	—64	178	—45	— 1
2	227	178	— 49	—	—	179	—48	203	—24	+ 7
3	236	—	—	196	—40	—	—	246	+10	+ 6
4	172	158	— 17	122	—53	—	—	131	—41	—15
5	266	—	—	250	—16	244	—22			—11
6	230	159	— 71	131	—99	168	—62			—11
7	337	187	—150	250	—87	308	—29			— 2
8	186	187	— 1	194	— 8					—10
9	206	132	— 74	162	—44					0
10	205	154	— 51							— 2
11	306	199	—107							+ 1
12	224	234	+ 10							+ 4

TABLE 2.—*Change in Serum Cholesterol in Hypercholesteremic Patients after Administration of Benzmalacene*

Patients (case no.)	Serum cholesterol (mg. per cent)									Weight change (lbs.)
	Mean control cholesterol	1 month	Change	2 months	Change	3 months	Change	4 months	Change	
13	498	530	+ 32	—	—	525	+ 27			0
14	560	374	—186	356	—204	342	—218	277	—283	—1
15	378	361	— 17	412	+ 34	394	+ 16	272	—106	+7
16	293	262	— 31	258	— 35	197	— 96	215	— 78	—8
17	430	481	+ 51	556	+166	422	— 8			+3
18	410	320	— 90	271	—139					+1
19	459	421	— 38	345	—114					—3

in serum cholesterol levels when given Benzmalacene for 1 month (table 1). Three patients (cases 10, 11, and 12) could not tolerate the drug because of gastrointestinal side effects and it was discontinued after 1 month. Serum cholesterol was maintained lower than control levels in all but 2 of the remaining 9 patients in whom administration of the drug was continued for 2 to 4 months.

Administration of Benzmalacene to Patients with Elevated Serum Cholesterol Levels. All of the 7 patients with abnormally elevated serum lipid levels had had stable serum cholesterol levels for several months prior to treatment. One patient (case 14) exhibited a profound fall in serum cholesterol when given Benzmalacene; this decrease persisted throughout the treatment period of 4 months (table 2). In addition, a marked rise in the triglyceride fraction, a fall in the total cholesterol to phospholipid ratio, and rise in ratio of free cholesterol to total cholesterol were noted (table 3). Another patient (case 15) had no change in serum cholesterol for 3 months; after 4 months of therapy a sharp drop in serum cholesterol was noted for the first time. Associated with the decrease in serum cholesterol of over 100 mg. were changes in other lipid fractions similar to those noted in case 14.

In 2 patients (cases 13 and 17) serum cholesterol levels showed little change. The remaining 3 patients (cases 16, 18, and 19) continued to maintain serum cholesterol levels lower than control values while taking the drug for 2 to 4 months.

Side Effects from Benzmalacene. Of 19 patients, 3 were uncomfortable from mild

TABLE 3.—*Changes in Lipid Fractions after Treatment with Benzmalacene for Four Months*

	Patient			
	Case 14		Case 15	
	Control	After treatment	Control	After treatment
Total cholesterol (mg. %)	560	277	378	272
Triglycerides	228	714	247	434
Total cholesterol/ phospholipid	1.34	0.69	1.07	0.77
Free cholesterol/ total cholesterol	0.25	0.42	0.28	0.45

TABLE 4.—*Liver Function Following Administration of Benzmalacene*

Patient (case no.)	Duration of treatment (months)	Serum alkaline phosphatase (Bodansky units)	Bromsulfalein (% dye retained 45")
18	2	1.4	8
19	2	1.8	3
5	3	1.9	18
6	3	1.8	1
17	3	2.3	2
1	4	1.1	7
2	4	1.6	10
3	4	3.7	6
4	4	2.2	14
14	4	2.3	20
15	4	1.9	6
16	4	1.7	2

nausea, epigastric discomfort, and diarrhea; symptoms were often relieved by reduction of the daily dose of Benzmalacene from 1.0 Gm. to 0.5 Gm. Five patients were so disabled by gastrointestinal symptoms that administration of the drug was discontinued after 1 to 2 months. Symptoms when present usually persisted throughout the treatment period. Five of the hypertensive patients had weight loss of 11 to 15 lbs. during therapy; all of the 7 hypercholesteremic patients maintained a constant weight while taking the drug.

Liver function was measured at the end of the treatment period (2 to 4 months) in 12 patients (table 4). Serum alkaline phosphatase was within normal limits in all. Abnormal retention of bromsulfalein dye (more than 5 per cent after 45 minutes) was noted in 8 of 12 patients and was usually greater in those patients with the longer treatment period.

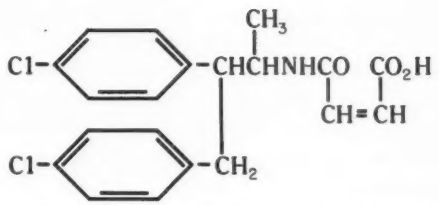

FIG. 1. Structural formula of Benzmalacene.

DISCUSSION

The problem of the desirability of lowering blood cholesterol by preventing its synthesis is a highly complex one. The multiplicity of derivatives of cholesterol necessary for the proper functioning of the body is now appreciated. Whether the level of cholesterol itself can be lowered without concurrently seriously disturbing the functional levels of its derivatives remains to be determined.

Clearly Benzmalacene can lower blood cholesterol levels for long periods without marked changes in body weight but liver function as measured by dye retention slowly but progressively becomes disturbed. While slow in onset, the liver dysfunction could become serious, therefore after a maximum of 4 months the drug was discontinued. We were unable in this period of time to detect other cognate changes in the patients.

Gastric burning, pain, nausea, and diarrhea occurred in some patients requiring discontinuance of the drug; in others, these symptoms were hardly noticeable.

In 2 patients the serum lipid pattern was studied by Dr. Helen Brown. It was shown that approximately 5 months after beginning the drug the total cholesterol had fallen significantly but concurrently the triglycerides had risen, along with the ratio of free to total cholesterol. But the ratio of total cholesterol to phosphatide fell sharply. These changes were profound. Without further studies we can no more than guess their significance. For our current purpose, the change underscores the capacity of drugs such as

Benzmalacene to alter the lipid economy of the body for better or for worse.

We believe that drugs such as this one should be carefully studied in animals for long periods and in a few select patients before they are used in the hopes of preventir., atherosclerosis.

Summary

Benzmalacene [N-(1-methyl-2,3-di-p-chlorophenylpropyl-maleamic acid)] effectively lowers blood cholesterol levels in most hypertensive patients but with some weight loss. Cholesterol was lowered in some hypercholesteremic patients but not in all and this occurred without weight loss. In 2 hypercholesteremic patients a sharp rise in triglycerides occurred while the cholesterol : phospholipid ratio fell and the free : total cholesterol ratio rose. Liver function as measured by bromsulfalein after 4 months' treatment had deteriorated in 8 of the 12 patients studied. Nausea, epigastric discomfort, and diarrhea were on occasion sufficiently discomforting to require discontinuing the drug. Drugs that interfere with cholesterol synthesis should be studied with great care for long periods before their widespread use in an attempt to prevent atherosclerosis.

Summario in Interlingua

Benzmalacena reduce efficacemente le nivellos sanguinee de cholesterol in le majoritate del patientes hypertensive, sed illo effectua un leve perdita de peso. Le nivellos de cholesterol esseva reducite in alicun patientes con hypercholesterolemia, sed non in omnes, e isto occurreva sin perdita de peso. In 2 patientes con hypercholesterolemia un marcate augmento de triglyceridos occurreva, durante que le proportion de cholesterol a phospholipido descendeva e le proportion de chotesterol libere a cholesterol total montava. Le function hepatic, mesurate per bromosulfaleina post 4 menses de tractamento, se monstrava deteriorate in 8 ex 12 patientes studiate. Nausea, disconforto epigastric, e diarrhea esseva a vices sufficientemente disturbante pro requirer le interruption del therapia. Drogas que disrumpe le synthese de cholesterol deberea esser studiate cautissimemente e durante prolongate periodos de tempore ante que illos es usate extensemente como agentes in le prevention de atherosclerosis.

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Correlation of Clinical and Hemodynamic Findings in Patients with Systemic Arteriovenous Fistulas

By JOSEPH J. MUENSTER, M.D., JOHN S. GRAETTINGER, M.D., AND JAMES A. CAMPBELL, M.D.

Although studies of the pathologic physiology of arteriovenous fistula have been reported, the circulatory responses to exercise and the nature of the syndrome resembling congestive heart failure have not been elucidated.

THE alterations in the circulation caused by a systemic arteriovenous fistula have been studied extensively[1-19] and the occasional occurrence of a syndrome resembling congestive heart failure in the presence of a chronic fistula has long been recognized.[20-23] In recent years cardiac catheterization has permitted more thorough study of such patients[14, 15] but concomitantly, since the potential hazard of the lesion has been better appreciated, early surgical correction of the defect has usually been carried out. Cardiac failure resulting from peripheral arteriovenous fistula therefore is now a rare entity and to our knowledge hemodynamic studies have been performed in only 2 cases presenting congestive heart failure.[15]

In the present paper studies before and after operation in patients with arteriovenous fistulas are reported. Two patients were in a state of congestive heart failure without apparent cause other than the fistula. The physiologic data observed in the patients with congestive heart failure not only clearly separated them from the others but also qualitatively resembled in many respects data obtained in patients with congestive failure resulting from primary myocardial disease.

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Done during Dr. Muenster's tenure of a James B. Herrick Fellowship in Cardiology.

MATERIAL AND METHODS

The fistulas in 4 patients had been present from 10 to 23 years; 2 were of recent onset (S.A., J.E.). In 5 cases the shunt was located in either the iliac or femoral vessels and in the sixth the brachial vessels were involved (J.E.). In 1 (J.P.) the shunt was congenital; the remainder were traumatic in origin resulting from either gunshot or stab wounds. Following physiologic studies surgical repair of the fistula was performed for the 5 acquired lesions. The diameters of the fistulas as estimated or measured by the surgeons at the time of surgery fell within a range of 1.0 to 1.5 cm. The proximal artery was dilated and tortuous in each of the patients in whom surgery was performed with the exception of patient S.A., whose shunt had been functional less than 2 weeks. In no case was there evidence of constriction by scar or surrounding fibrous tissue. Arteriography demonstrated similar tortuosity and dilatation and presumably a shunt of comparable size in the case of J.P. who had congenital lesions for which surgery was not performed.

The 2 patients (S.A., J.E.) whose fistulas were of relatively short duration are referred to as "short-term non-failure" patients and the other 2 without congestive failure whose fistulas had been functional for 18 and 19 years as the "long-term non-failure" patients (E.W., J.P.). The clinical histories of these 4 patients contained no symptoms suggestive of congestive failure. The 2 long-duration patients were laborers who were working without limitation until the time of their hospital admissions for study and elective surgery. The physical examination in each case revealed swelling and a bruit at the site of the fistula with venous engorgement in the affected

extremities, but no edema. Examinations of the heart and teleroentgenograms in 3 patients were entirely normal; 1 of the long-term patients (E.W.) had moderate enlargement of the heart and a grade III systolic apical murmur. Following surgery the murmur disappeared and the heart size returned to normal. Hemoglobin values were within normal limits in all patients. Blood volumes were normal in the 2 "short-term" and elevated in the 2 "long-term non-failure" patients.

The histories and findings of the 2 cases which we refer to as the "failure patients" differed markedly from the group above.

The first patient (C.J.) was a 41-year-old Negro woman who had been shot in the left upper thigh 19 years prior to admission. Slight swelling of the entire extremity had persisted throughout the years. Eighteen months prior to admission at our initial examination she had no complaints or signs of cardiovascular disease except for the arteriovenous fistula. Her blood pressure was 120/80 and the heart rate was 80 per minute. At that time she refused surgical correction. About 2 months prior to admission she noted an increase in the edema of the affected extremity and the onset of edema of the other limb. At this same time she began to experience shortness of breath on exertion, palpitation, and a nonproductive cough which was worse in the recumbent position, and she noted a rapid increase of her body weight.

Physical examination revealed an obese, orthopneic woman with a blood pressure of 158/102 and a heart rate of 120 per minute. Her neck veins were distended, the hepatojugular reflux was positive, and moist fine rales were present in both bases. A grade-II apical systolic murmur and a protodiastolic gallop rhythm were noted with an increased second sound at the pulmonic area. The liver was palpable 4 cm. below the costal margin. There were moderate edema of the right leg to the level of the midcalf and marked pitting of the left limb to the inguinal region. A thrill and a bruit were present in the area of the lesion in the upper left thigh. The Nicoladoni-Branham bradycardiac sign was demonstrable.[24, 25] The protodiastolic gallop rhythm disappeared while the fistula was compressed.

The arm-to-tongue circulation time was 60 seconds (Decholin). The venous pressure was 300 mm. of saline. The chest x-ray disclosed clouding of the lower half of the left lung field and a shift of the mediastinum to the left as a sequel to collapse therapy for tuberculosis. The left cardiac border could not be identified. The vascular markings in the right lung field were increased. The electrocardiogram was consistent with left ventricular hypertrophy. The hemoglobin was 12.5 Gm. per cent. Following physiologic studies she was treated with bed rest and sodium restriction for 2 weeks prior to surgery. She lost 17 pounds and the edema of the right leg disappeared as did the signs of pulmonary edema. Blood volume preoperatively was 29 per cent above predicted. Re-anastomosis of both the femoral artery and vein was successfully accomplished. She had a diuresis of 4,700 ml. of urine during the first 24 hours following surgery. Her total weight loss was 33 pounds, and a 1,000 ml. decrease in blood volume had occurred 13 days after surgery. Five months following study she was fully active without symptoms; her blood pressure was within normal limits.

The second patient in failure (R.A.) was a 47-year-old Negro who had been stabbed in the right thigh 23 years prior to admission. Since that time he had noted a pulsating mass in the region of the scar. His service in the army during World War II included combat duty. On examination 7 years prior to study the blood pressure was 146/80 and the cardiac examination, including chest x-ray, was normal. For the 3 to 4 months preceding study he had noted steadily increasing exertional dyspnea, edema, and weight gain. Examination revealed a moderately dyspneic man with a blood pressure of 150/80 and heart rate of 93. Moderate cardiac enlargement, a protodiastolic gallop and a grade-II apical systolic murmur were noted. The liver was enlarged 6 cm. below the right costal margin. A pulsating mass and a thrill were present over the lesion in the right midthigh. Moderate edema of the left leg to the midthigh and marked edema of the right leg extending to the inguinal region were present. The Nicoladoni-Branham sign was demonstrable and the protodiastolic gallop disappeared during compression. The arm-to-tongue circulation time (Decholin) was 40 seconds; venous pressure was 270 mm. of water. Fluoroscopy and teleroentgenograms revealed enlargement of the left ventricle, right ventricular outflow tract, and increased pulmonary vascular markings with small pleural effusions bilaterally. Hemoglobin was 13 Gm. per cent. An electrocardiogram disclosed only low voltage of the T waves. After physiologic studies the patient was treated with bed rest, digitalis, mercurial diuretics, and sodium restriction for 30 days. On this regimen he lost 10 pounds, edema disappeared, blood pressure and heart rate returned to normal but blood volume changed only from 65 to 56 per cent above the predicted value. Re-anastomosis of the femoral artery was then performed and the femoral vein ligated. Postoperatively he developed bacterial endocarditis and consequent aortic regurgitation.

Despite this complication 2½ months after surgery he was active and asymptomatic; the cardiac silhouette and lung fields were within normal limits. His total weight loss was 15 pounds.

The studies were performed in an air-conditioned room on patients in the postabsorptive state, usually after a sedative dose of sodium allyl barbiturate. Details of the methods used in this laboratory have been previously described.[26] In 3 cases observations were made with the shunt totally occluded by direct pressure. Blood volume studies were made with Evans blue dye (T-1824) or with I^{131} tagged albumin. A correction of 0.92 was used for total body hematocrit level. The same method was used in a given patient for each serial study.

Results

The data obtained during these studies are shown in table 1.

Cardiac Output

The cardiac output in the resting state was abnormally high in each patient. During exercise a qualitatively normal increase in cardiac index was observed in the 2 short-term non-failure patients (S.A., J.E.). The exercise response was less than normal in one long-term non-failure patient (E.W.) and insignificant in the other (J.P.). A decrease in cardiac output during exercise occurred in the 2 failure patients.

Five patients were restudied after surgery and in each instance the resting cardiac output was considerably lower than the preoperative value and a normal increase occurred during exercise.

Stroke Volume and Heart Rate

The elevation in cardiac output at rest in 3 of the 4 non-failure patients was caused by an increase of both stroke volume and heart rate. In the fourth patient (E.W.) a markedly increased stroke volume was accompanied by a normal heart rate. In the failure patients the cardiac output elevation at rest was more attributable to a tachycardia than to elevation of stroke volume and a marked drop in stroke volume occurred during exercise.

Arteriovenous Oxygen Difference

A markedly reduced arteriovenous oxygen difference was found in each patient regardless of the presence or absence of clinical heart failure. During exercise the arteriovenous oxygen difference remained abnormally narrowed. Thus both at rest and during exercise the cardiac output was greater than expected on the basis of oxygen consumption.

Central and Peripheral Venous Pressures

The systemic venous and right atrial pressures of the 4 non-failure patients were within normal limits and during exercise the increases in cardiac output occurred without significant changes in atrial pressure. The venous and right atrial pressures were greatly elevated in the 2 patients with congestive failure and a further rise of atrial pressure was observed in each during exercise. After surgery the venous and atrial pressures in each patient were within normal limits.

Systemic Arterial Pressure and Total Systemic Resistance

Systemic arterial pressure was low normal in one short-term non-failure patient (S.A.) and high normal in the other, J.E.; systemic resistances were reduced. Postoperatively the pressures and resistances were unchanged in the patient whose fistula had been only of 8 days' duration and, in the other, resistance was restored to normal.

In one long-term non-failure patient (J.P.) pressure was high normal and resistance reduced. In the other, E.W., arterial pressure was low and resistance was remarkably low; compression of the fistula in this patient resulted in a 2-fold increase of diastolic and mean arterial pressure. After surgery pressure was normal and resistance had increased. The data in the 2 failure patients distinctly differed from the non-failure patients. Systemic hypertension was present and systemic resistances were markedly higher than were found in the non-failure group; during exercise a marked rise in systemic resistance occurred. Postoperatively, mean

TABLE 1.—*Hemodynamic Data*

Patient	Duration of fistula	Study	Age — sex	Surface area — $M.^2$	Oxygen consumption (ml./min./$M.^2$)		Cardiac index (L./min./$M.^2$)		Cardiac output (L./min. × 100) / Oxygen consumption (ml.)		Stroke index (ml./beat/$M.^2$)		Heart rate (beats/min.)		A-V oxygen difference (ml./100 ml.)		Mean right atrial pressure (mm. Hg)		Mean pulmonary arterial pressure (mm. Hg)		Systemic pressure (mm. Hg)				Total pulmonary resistance (dyne cm.$^{-5}$ sec.)		Total systemic resistance (dyne cm.$^{-5}$ sec.)		Total blood volume (ml.)	Plasma volume (ml.)
					R	E	R	E	R	E	R	E	R	E	R	E	R	E	R	E	R S/D	R M	E S/D	E M	R	E	R	E		
S.A.	8 days	preop.	21-M	1.62	159	379	5.52	7.90	3.47	2.08	55	66	100	120	2.87	4.80	6	—	19	18	127/44	85	153/78	103	170	112	759	644	3742	2470
		postop. (14 days)		1.59	145	284	4.39	5.65	3.03	1.99	65	64	68	88	3.31	5.03	5	4	12	15	106/58	75	120/60	78	137	133	859	693	4043	2547
J.E.	6 weeks	preop.	30-M	1.80	171	388	8.88	11.56	5.19	2.98	74	89	120	130	1.92	3.36	8	8	32	30	154/78	112	136/74	102	160	115	560	392	5202	2913
		postop. (6 weeks)		1.82	120	317	3.08	4.35	2.57	1.37	39	50	78	87	3.87	7.28	4	4	20	20	135/82	111	156/96	120	285	204	1581	1225	—	—
E.W.	18 years	preop.	32-M	1.91	159	300	8.53	9.81	5.36	3.27	140	129	61	75	1.86	3.06	2	—	18	22	107/46	69	136/59	93	88	94	339	377	6789	4006
		*comp.											40						16		172/90	110							—	—
		†albumin			164	312	7.83	10.76	4.77	3.45	131	145	60	76	2.10	2.90	—	6	24	30	122/55	81	138/65	91	128	117	433	354	7417	4747
		postop. (8 months)	33	1.98	195	346	4.22	6.29	2.16	1.82	77	87	55	72	4.62	5.51	-4	—	7	8	120/80	93	123/75	98	67	51	890	629	4835	2708
J.P.	19 years		19-M	2.06	153	226	6.59	7.00	4.31	3.10	72	73	92	96	2.32	3.23	—	11	15	20	156/88	113	159/105	120	88	111	665	665	6210	3726
Congestive failure																														
C.J.	10 years	preop.	41-F	1.78	143	169	5.62	3.76	3.93	2.22	41	27	138	140	2.55	4.48	21	24	67	69	190/105	138	186/104	143	536	823	1103	1706	5725	3492
		*comp.			139		3.00				22		135		4.64		—		80		210/120	159			1197		2380			
		postop. (13 days)		1.62	130	252	3.05	3.75	2.35	1.49	25	27	120	139	4.25	6.72	1	0	17	26	130/81	102	161/95	120	275	342	1650	1583	4750	2607
R.A.	23 years	preop.	47-M	1.70	125	211	4.84	4.20	3.87	1.99	49	37	98	114	2.59	5.03	20	31	37	47	164/86	120	170/94	134	356	523	1155	1746	6890	4369
		*comp.			142		2.86				34		84		4.98		—		46		225/112	155			756		2549			
		postop. (3 months)		1.67	158	516	2.75	7.77	1.74	1.51	33	54	83	145	5.75	6.64	6	8	26	32	134/62	98	193/87	136	453	197	1706	838	5068	3401

*Compression over site of fistula during preoperative study.

†After intravenous infusion of 100 Gm. of salt-free albumin.

arterial pressures and the systemic resistances were normal.

Pulmonary Arterial Pressure and Total Pulmonary Resistance

The total pulmonary resistances were low in the non-failure patients and pulmonary arterial pressures were high normal. The pressures and resistances were elevated in the 2 patients in congestive heart failure and a marked decrease in pulmonary arterial pressure was observed in each following surgery.

Discussion

The clinical state of congestive heart failure present in 2 of these patients was similar to the syndrome of congestive failure that has been observed by others in certain patients with arteriovenous fistulas.[20-23] Furthermore, it was similar to the syndrome of chronic congestive heart failure which may be present in patients suffering from heart disease of any etiology. Yet, after surgical excision of the fistulas, no heart disease was demonstrable in one of these 2 individuals and in the other a quite normal functional capacity and heart size were found despite the development of aortic regurgitation following postoperative acute bacterial endocarditis. Similar clinical sequences have been observed previously, but it has been proposed that this syndrome does not represent actual heart failure and is attributable to circulatory congestion simulating congestive heart failure without actual myocardial inadequacy.[27, 28]

The physiologic data obtained during and following the syndrome of congestive failure in these 2 patients, however, clearly indicate that actual myocardial inadequacy was present. Their cardiac outputs were relatively lower than those found in the 4 other patients with arteriovenous fistulas and significant elevations of venous, atrial, pulmonary arterial, and systemic arterial pressures were found at rest. During exercise their cardiac outputs fell to still lower levels and their intravascular pressures became more abnormal. With the exception of the absolute level of the cardiac output, the hemodynamic findings in these 2 individuals were, in fact, quite similar to those usually found in patients suffering from chronic congestive heart failure due to heart disease of any etiology.[29, 30] The physiologic data obtained postoperatively suggested, however, that no antecedent underlying heart disease had been present to explain the transient occurrence of clinical congestive heart failure; this syndrome therefore seemed to have been the result solely of transient heart failure produced by the systemic arteriovenous fistulas.

In these 2 patients, who had chronic congestive heart failure on clinical examination and myocardial inadequacy as measured by cardiac output and intravascular pressure observations, the duration and anatomy of the fistulas and collateral vessels did not differ importantly from those found in the 2 long-term non-failure patients and the magnitude of the compensatory hypervolemia was not markedly greater than in the long-term non-failure patient E.W. Myocardial inadequacy would, therefore, seem to have been the result of a finite ability of the myocardium to increase and maintain stroke volume in the face of the demand imposed by the decreased total peripheral resistance caused by the fistula and the increased venous return caused by the compensatory hypervolemia. As a result of myocardial inadequacy, lower cardiac outputs and elevated right atrial and pulmonary arterial pressures occurred.

Systemic arterial hypertension was also present in these 2 failure patients with elevation of the total systemic resistance to the normal range, despite the presence of the fistulas. The inadequate cardiac output resulting from the volume load apparently had as its consequence a generalized increase in systemic arteriolar resistance of sufficient magnitude to result in an increase in total systemic resistance to normal despite the locally low resistance of the fistula. In these patients maintenance of blood flow through the fistula in the face of a decreasing car-

diac output thus required vasoconstriction with a consequent reduction in the circulation to the remainder of the body.[18] Systemic hypertension in these individuals is therefore thought to have represented the consequence of an increased peripheral resistance due to heart failure in the presence of an overfilled circulation. Systemic hypertension has been reported in certain other patients with systemic arteriovenous fistulas and congestive heart failure but has not invariably been found.[15, 20–23] It would seem likely, therefore, that myocardial inadequacy developed initially from the volume load imposed by the fistulas and was subsequently augmented by the pressure load imposed by the hypertension that occurred as a consequence of the development of heart failure. The development of transient systemic hypertension during exacerbations of chronic congestive heart failure in patients with heart disease of various etiologies is well recognized. The severity of the hypertension that may result from an increase in total systemic resistance in the presence of hypervolemia is evident in the pressures obtained during occlusion of the fistulas in the 2 failure patients.[6]

In these 2 patients with systemic arteriovenous fistulas we suggest that maintenance of an adequate arterial pressure eventually required levels of cardiac output that their hearts could not sustain with the consequent development of myocardial inadequacy. The compensatory hypervolemia which, prior to the development of heart failure aided in the maintenance of an adequate arterial pressure, then became a deleterious mechanism, since it contributed to the volume load presented to the failing heart and to the development of the pressure load imposed by systemic hypertension. We see in the hypervolemia, therefore, an example of an essential homeostatic mechanism becoming an undesirable factor in the presence of heart failure.

Finally, in these individuals who had presented congestive heart failure, surgical correction of the peripheral circulatory lesion resulted in the apparent return of circulatory and myocardial function to normal. These data thus provide evidence that heart failure may be produced in the apparently healthy heart by a peripheral circulatory load and, furthermore, they also permit a description of the sequences and adjustments by which this may occur.

Summary

A correlation of clinical and hemodynamic data in 6 patients with systemic arteriovenous fistulas has been presented. Two of the patients presented overt congestive failure. With the exception of the high absolute level of cardiac output, the decrease in cardiac output with exercise in the presence of elevated central venous pressure in the 2 patients with congestive failure was similar to the finding in patients with congestive failure of any etiology. Systemic hypertension occurred with the development of congestive failure despite the low resistance lesion of the fistula.

Myocardial inadequacy seemed to have been the consequence of a finite capacity of the heart to increase and maintain stroke volume in the face of the demand imposed by the low resistance lesion and the compensatory hypervolemia. Surgical correction of the fistulas resulted in return of circulatory dynamics to normal. These data, therefore, provide evidence that heart failure may be produced in the apparently healthy heart by a peripheral circulatory load.

Acknowledgment

Patient R. A. was studied through the courtesy of Dr. L. A. Baker, former Chief of Medical Service, Veterans Administration Hospital, Hines, Illinois. The other patients were studied through the courtesy of their attending surgeons, Dr. O. C. Julian and Dr. F. V. Theis.

Summario in Interlingua

Es presentate un correlation del datos clinic e hemodynamic ab sex patientes con fistulas arterio-venose in le circulation systemic. Duo del patientes exhibiva patente disfallimento congestive. Con le exception del

alte nivello absolute del rendimento cardiac, le reduction del rendimento cardiac occurrente in exercitio in le presentia de elevate tensiones centro-venose in le duo patientes con disfallimento congestive in le presente studio esseva simile al constatationes in patientes con disfallimento congestive de non importa qual etiologia. Hypertension systemic occurreva con le disveloppamento de disfallimento congestive in despecto del basse resistentia occasionate per le fistulas.

Inadequatia myocardial esseva apparentemente le consequentia de un finite capacitate del corde pro augmentar e mantener le volumine per pulso in le presentia del requirimentos imponite per le lesion a basse resistentia e le hypervolemia compensatori. Le correction chirurgic del fistulas resultava in le retorno del dynamica circulatori a conditiones normal. Per consequente le datos hic presentate demonstra que disfallimento cardiac pote esser producite in apparentemente normal cordes per un carga in le circulation periphic.

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Exercise must be taken within the limits which each individual soon learns to recognize. In severe recurring attacks induced by slight muscular efforts, a period of absolute rest should be enjoined. The sudden, quick movements which rapidly increase the blood pressure and throw a strain upon the heart are the most dangerous; and most of all those with which are associated strong emotions. The patients should be urged to walk on the level, in the literal as well as metaphorical meaning of the phrase. He should learn "to live within the income of his circulation," with which wise saw from the lips of the late Dr. Sibson a friend with organic heart disease has been comforted and sustained for a quarter of a century.—WILLIAM OSLER, M.D. *Lectures on Angina Pectoris and Allied States*, 1897.

Intracardiac Phonocardiogram in Thirty Cases of Atrial Septal Defect

By GEORGE A. FERUGLIO, M.D., AND AKKAYA SREENIVASAN, M.D.

Thirty cases of atrial septal defect proved by cardiac catheterization, surgery, or postmortem examination have been investigated with the technic of intracardiac phonocardiography, which provided precise localization of the source of heart sounds and murmurs. The site and mechanism of origin of the many auscultatory signs in uncomplicated atrial septal defect and in cases of Lutembacher's syndrome, tricuspid atresia, and persistent atrioventricular canal were elucidated by direct intracardiac sound recordings and simultaneous external chest phonocardiograms.

THERE have been many recent reports of the auscultatory features of atrial septal defect and these have been reviewed both clinically and with the aid of chest phonocardiography.[1-7]

The commonest auscultatory findings in uncomplicated atrial septal defect are a basal systolic ejection murmur, usually soft, and a wide, fixed splitting of the second sound over the pulmonary area. Less frequently an early blowing diastolic murmur is heard at the base and along the left sternal border in the second and third left intercostal spaces. At the apex, or medial to it, systolic and diastolic murmurs may occasionally be present, together with an accentuated first sound. The systolic apical murmur is usually of regurgitant type (pansystolic); the diastolic apical murmur occurs in mid-diastole or in presystole.

There appears to be no general agreement about the site and mechanism of production of these signs. The relative importance of various factors such as the flow across the atrial septal defect, the increased flow through the tricuspid and pulmonary valves, and the anatomic changes in the mitral and tricuspid valves, has not been established with certainty.

The purpose of this study was to contribute to a better understanding of the site and mechanism of production of the altered heart sounds and murmurs in atrial septal defect with the help of intracardiac sound recording.

The technic originally described by Lewis et al.[8] for intracardiac phonocardiography has been used. Precise localization of the sources of sounds and murmurs is possible with the aid of a barium titanate microphone incorporated in the leading tip of a specially designed catheter. Some intracardiac phonocardiograms by this and other technics in cases of atrial septal defect have been reported.[9-12]

Material and Methods

Thirty cases of proved atrial septal defect are included in this study: 18 were male and 12 female, and they ranged in age from 3 to 54 years, the majority being in the second and third decade of life. The diagnosis of atrial septal defect was made on clinical, radiologic, and electrocardiographic grounds and was proved by right heart catheterization, during which the defect was crossed in 28 of the 30 cases. Further confirmation was obtained in patients who underwent surgical repair (22 patients, including the 2 in whom the septal defect was not crossed by the catheter) or who succumbed (2 patients) and were examined post mortem (table 1).

To confirm clinical auscultation, a routine chest phonocardiogram was recorded with the aid of a 2-channel photographic apparatus (Twin-Beam,

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TABLE 1.—*Diagnosis in Thirty Cases of Atrial Septal Defect*

Diagnosis	Proved by catheter	Confirmed by Surgery	Confirmed by Post mortem
Ostium secundum defect	20	16†	—
Ostium primum defect	4	3	1
Lutembacher's syndrome	2	2	—
Persistent atrioventricular canal	2	1	1
Tricuspid atresia	2*	—	—

*Confirmed by angiocardiography.

†In 4 cases fibrous strands were found across the defect.

TABLE 2.—*Clinical Auscultatory Signs in 28 Cases of Atrial Septal Defect*

Auscultatory signs	No. of cases
Loud first sound	22
Split second sound: not fixed	5
fixed	23
Basal systolic murmur	28
Basal early diastolic murmur	4
Apical systolic murmur	4
Apical diastolic murmur: mid	5
late	3

Sanborn). The findings, excluding the 2 cases of tricuspid atresia, are summarized in table 2.

In both cases of tricuspid atresia (ages 3 and 6 years), a loud apical first sound and a mid-diastolic murmur with presystolic accentuation were recorded. In addition, in 1 case a harsh pansystolic murmur was recorded in the third and fourth left intercostal space. The second sound at the base was rather loud and single in both cases, and was preceded by a soft ejection systolic murmur.

Physiologic studies (right heart catheterization, dye-dilution studies, oximetry during exercise)[21] showed that all 24 patients with uncomplicated atrial septal defect had a predominantly left-to-right shunt. Blood flow measurements obtained by the Fick principle showed that while the systemic flow was within the normal range in all these cases, the pulmonary flow was 2 to 3 times the systemic flow in 8 instances, and over 3 times the systemic flow in the remaining 16. In the 4 cases of Lutembacher's syndrome and persistent atrioventricular canal, the systemic flow was normal, while the pulmonary flow was over 3 times the systemic flow. In the 2 cases of atrial septal defect with associated tricuspid atresia, there was increased flow across the mitral valve.

The intracardiac phonocardiograms were recorded with the aid of a specially designed phonocatheter, a preamplifier,* and a phonocardiograph. The phonocatheter consisted of a sound transducer (a hollow cylinder of activated barium titanate, 1.5 mm. in diameter and 15 mm. long), soldered to a coaxial cable. The catheter had a plastic coating, which prevented direct contact of the transducer with the blood and inner walls of the heart and vessels (a possible source of artifact), and allowed chemical sterilization of the apparatus. The frequency response of the sound transducer ranged from 5 to 10,000 c.p.s. The preamplifier, to which the acoustical signals of the catheter were fed, provided linear amplification for the same frequencies. Tracings were recorded with the aid of a photographic 2-channel and a photographic 3-channel phonocardiograph used for routine clinical phonocardiography.

The sound catheter, which was clearly seen on fluoroscopy because of its metallic components, was introduced into the cavities of the heart and pulmonary artery by the technic of venous catheterization. Reference marks were placed on the screen during routine catheterization, to locate the pulmonary, tricuspid, and mitral orifices. Intracardiac phonocardiograms were recorded in the right, left, and main pulmonary arteries; in 3 different positions in the right ventricle and right atrium; and in the left atrium and left ventricle in the 24 cases in which the septal defect was crossed by the "sound" catheter. Continuous recordings were also made during the withdrawal of the catheter across the pulmonary, tricuspid, and mitral valves and across the atrial septal defect. In addition to intracardiac sounds, simultaneous external chest phonocardiograms were recorded for comparison.

*Phonocatheters and preamplifiers were built and made available to the authors by the U.S. Naval Air Development Center of Johnsville, Pa.

RESULTS

In the analysis of the intracardiac phonocardiograms obtained in the cases of uncomplicated atrial septal defect, the following features were encountered.

Within the pulmonary artery were recorded an ejection type of murmur of varying intensity and a loud pulmonary closure occurring 0.04 to 0.06 second after the aortic closure (fig. 1). During inspiration both the murmur and the sound increased in intensity in 15 cases and remained unchanged in 9.

A further delay in the pulmonary closure during inspiration was observed in 2 cases.

Within the right ventricle in all cases was recorded a loud tricuspid closure occurring 0.06 to 0.08 second after the onset of the QRS complex. Simultaneous intracardiac and external recordings from the apical region (fig. 2) showed that the maximal vibrations of the first sound on the chest phonocardiogram occurred at the time of the loud tricuspid closure. In addition to a loud first sound, in the inflow tract of the right ventricle a diastolic murmur was recorded in 9 cases. This murmur was mid-diastolic in 5 instances (fig. 3), presystolic in 4 (fig. 4), and increased slightly in intensity during inspiration. Only in 6 cases similar mid-diastolic or presystolic murmurs were observed in simultaneous external phonocardiograms from the apical region. In 4 instances an early diastolic murmur "decrescendo" in type, was recorded in the outflow tract of the right ventricle just beneath the pulmonary valve. A similar murmur was observed in simultaneous external phonocardiograms from the second and third intercostal spaces (fig. 5) in all 4 instances. No murmurs were recorded in the right ventricle (fig. 1) in 11 cases.

The 2 patients with Lutembacher's syndrome, who underwent surgical repair of the septal defect and the mitral stenosis, had the intracardiac phonocardiographic features of uncomplicated atrial septal defect in the right side of the heart. In only one of these could the sound catheter be advanced through the septal defect into the left side of the heart. In this case, in which atrial fibrillation was present, a mid-diastolic murmur (fig. 6) was recorded in the inflow tract of the left ventricle and no murmurs were recorded in the left atrium. In spite of the mitral stenosis a significant pressure gradient across the mitral valve was not demonstrated. The systemic blood flow in this case was at the lower limits of normal.

In the 2 cases of tricuspid atresia, the sound catheter as well as the ordinary catheter, entered only the right and left atria and the left ventricle. No murmurs were recorded within the atrial chambers. Within the inflow tract of the left ventricle a mid-diastolic murmur with presystolic accentuation was present (fig. 7). In both cases there was no significant pressure gradient across the mitral valve.

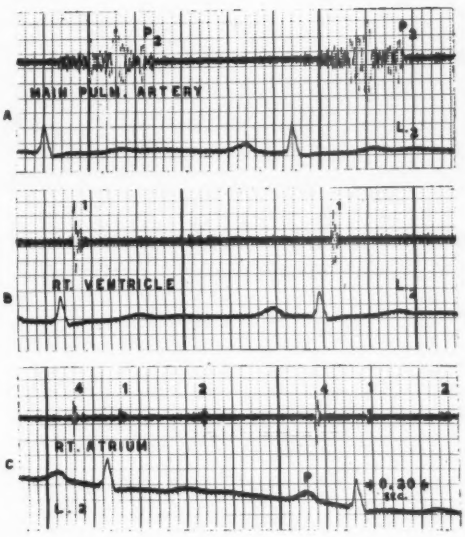


FIG. 1. Intracardiac phonocardiogram in a 19-year-old girl with uncomplicated atrial septal defect. *A*, systolic ejection murmur of moderate intensity within the pulmonary artery; *B*, loud tricuspid closure in the right ventricle; *C*, soft first and second sound, and a fourth sound in the right atrium.

In cases of uncomplicated atrial septal defect, of Lutembacher's syndrome, and of tricuspid atresia, in which the phonocatheter was advanced into the left atrium, no murmur was observed on continuous recordings during withdrawal of the catheter across the septal defect.

In the 2 cases of presistent atrioventricular canal, in addition to an ejection murmur within the pulmonary artery, a loud pansystolic murmur was recorded in the outflow tract of the right ventricle. In addition, a regurgitant systolic murmur was recorded in the atrial chambers in the proximity of the atrioventricular valves (fig. 8).

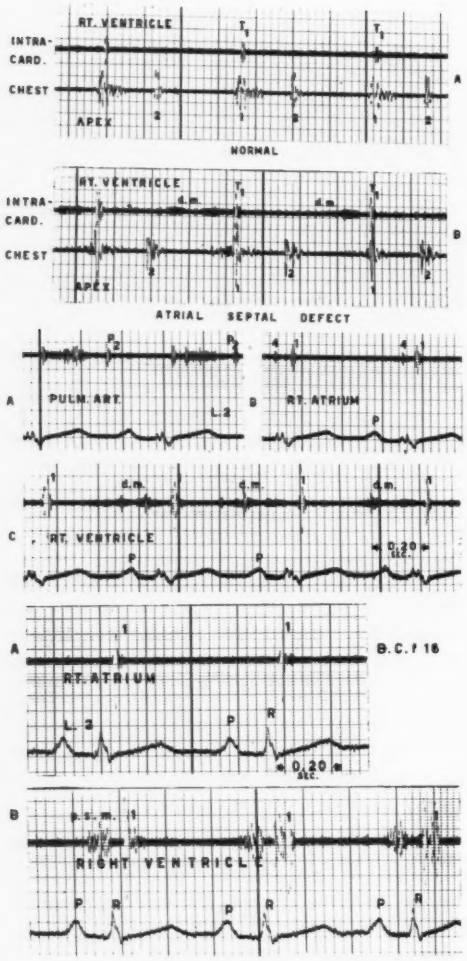


FIG. 2 *Top.* Simultaneous recordings from within the right ventricle by the phonocatheter and externally from the apical region in a normal subject *A*, and in a patient with uncomplicated atrial septal defect *B*.

FIG. 3 *Middle.* Intracardiac phonocardiogram in a case of uncomplicated atrial septal defect. *A*, systolic ejection murmur within the pulmonary artery; *B*, no murmurs within the right atrium; *C*, loud tricuspid closure and a mid- and late diastolic murmur within the inflow tract of the right ventricle.

FIG. 4 *Bottom.* Uncomplicated atrial septal defect with, *A*, no murmur within the right atrium, *B*, a loud tricuspid closure and a presystolic murmur within the inflow tract of the right ventricle.

Postoperative Studies. Twelve patients were reinvestigated 4 to 10 weeks postoperatively; no evidence of shunt was found by oximeter after exercise or dye-dilution studies and there was no pressure gradient across the pulmonary valve. The intracardiac phonocardiogram showed changes. Within the pulmonary artery the systolic murmur decreased considerably in intensity. The second sound also decreased in intensity but there were no significant changes in the delay of the pulmonary valve closure. Within the right ventricle the mid-diastolic and presystolic murmurs disappeared with no exception. In 2 cases, an early diastolic murmur was still present in the outflow tract of the right ventricle.

DISCUSSION

It is generally accepted that the commonest auscultatory finding in atrial septal defect is a basal systolic murmur.[1-6] This murmur was thought to be due to flow across the defect[13] or dilatation of the pulmonary artery[14] or to the increased flow through the pulmonary valves.[5, 6] The last hypothesis was strengthened by the observations of Soulié et al.,[10] Feruglio and Dalla Volta,[15] and Luisada and Testelli,[11] who recorded a systolic murmur within the pulmonary artery in cases of uncomplicated atrial septal defect by means of different intracardiac phonocardiographic technics.

A systolic murmur, localized within the pulmonary artery, was also the most common and striking intracardiac phonocardiographic abnormality observed in the present series. This was the only murmur recorded in 15 of the 24 cases of uncomplicated atrial septal defect. In simultaneous recordings from within the pulmonary artery and externally from the second and third left intercostal spaces, this murmur appeared with the same characteristics of frequency, shape, and duration (fig. 9). The absence of any other systolic murmur in the 4 cavities of the heart and the close similarity between intracardiac and external recordings confirm the idea that the basal systolic murmur

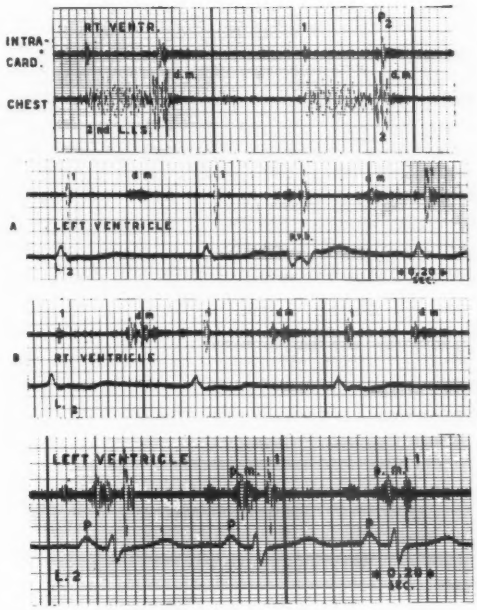
in uncomplicated atrial septal defect is produced in the pulmonary artery.

On the intrapulmonary phonocardiogram, as in the external phonocardiogram, this murmur had the features of a flow murmur. It was high pitched, had a midsystolic accentuation, and ended before the pulmonary closure. Its intensity had good correlation with the estimated pulmonary blood flow and decreased considerably after surgical correction of the defect. The predominant factor in the mechanism of production of the basal systolic murmur in atrial septal defect therefore seems to be increased blood flow through the pulmonary valve.

In the 4 cases in which an early basal diastolic murmur was present on external recordings a similar murmur was recorded in the intracardiac phonocardiogram from the upper outflow tract of the right ventricle, suggesting pulmonary insufficiency as the mechanism of production of this murmur. This substantiates the hypothesis of Barber et al.[1] and Leatham and Gray.[5]

There is great diversity of opinion regarding the source and mechanism of the apical mid-diastolic and the presystolic murmurs in atrial septal defect. The possibilities suggested are an associated mitral stenosis,[16–18] flow across the septal defect,[1, 19, 20] and increased flow through the tricuspid valve.[5, 21] In this series diastolic apical murmurs were recorded on routine chest phonocardiograms in 10 cases, which included 2 cases of associated mitral stenosis and 2 cases of tricuspid atresia.

The intracardiac phonocardiogram was most helpful in localizing the source and mechanism of production of these apical diastolic murmurs. In the uncomplicated atrial septal defect presystolic and mid-diastolic murmurs were localized to the inflow tract of the right ventricle. This confirms the view that the murmurs originate at the tricuspid valve. Subsequent to the surgical correction of the defect, these murmurs disappeared in the intracardiac phonocardiogram, strongly suggesting that their mechanism of production is the increased flow through the tricuspid valve.



TRICUSPID ATRESIA

FIG. 5 *Top.* Simultaneous recordings from within the outflow tract of the right ventricle (by the phonocatheter) and externally from the second left intercostal space in a case of uncomplicated atrial septal defect.

FIG. 6 *Middle.* Intracardiac phonocardiogram in a man aged 57 with Lutembacher's syndrome (proved by surgery) and atrial fibrillation. *A*, a mid-diastolic murmur is recorded in the inflow tract of the left ventricle, and also *B*, in the inflow tract of the right ventricle.

FIG. 7 *Bottom.* Intracardiac phonocardiogram in a boy aged 6 with tricuspid atresia. A mid-diastolic murmur with presystolic accentuation is recorded in the inflow tract of the left ventricle, due to increased flow across the mitral valve.

In the 2 cases of tricuspid atresia the same mechanism of increased flow across the mitral valve probably accounts for the presence of the diastolic murmur in the inflow tract of the left ventricle.

In the case of Lutembacher's syndrome with atrial fibrillation, a mid-diastolic murmur was recorded in the inflow tract of the left ventricle, although neither appreciable pressure gradient nor increased flow was

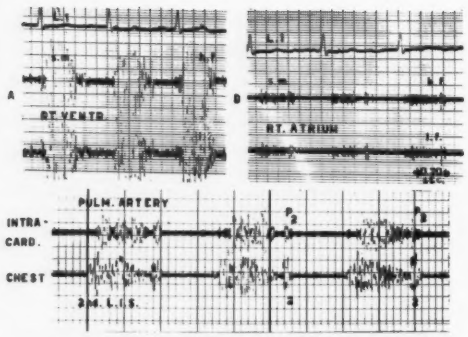


FIG. 8 *Top.* High and low frequency (*h.f.,l.f.*) intracardiac phonocardiogram in a 5-year-old boy with persistent atrioventricular canal. *A,* a loud pansystolic murmur in the outflow tract of the right ventricle; *B,* a regurgitant systolic murmur in the right atrium.

FIG. 9 *Bottom.* Simultaneous recordings in a case of uncomplicated atrial septal defect from within the pulmonary artery (by phonocatheter) and externally from the second left interspace, showing a close similarity in the systolic murmur recorded from both sites.

demonstrable across the mitral valve. This intracardiac phonocardiographic finding alone led to the diagnosis of associated mitral stenosis, which was confirmed later at surgery. It is of interest that in this case a mid-diastolic murmur was present in the inflow tract of the right ventricle as well, probably due to increased flow across the tricuspid valve. It was not possible to differentiate this murmur on the chest phonocardiogram from the similar diastolic murmur recorded in the inflow tract of the left ventricle.

The intracardiac phonocardiographic features in persistent atrioventricular canal were a loud pansystolic murmur within the outflow tract of the right ventricle and a systolic regurgitant murmur in the artial chambers in the proximity of the atrioventricular valves. Flow due to an interventricular shunt is responsible for the former pansystolic murmur and the incompetence of the atrioventricular valves is responsible for the latter regurgitant murmur. In no instance, other than in these 2 cases of persistent atrioventricular canal, were murmurs recorded within the right or left atrium or during pullback of the sound catheter across the atrial septal defect, including the 4 cases in which, at surgery, strands across the defects were found. This observation probably means that the flow across the defect in either direction is silent. The intracardiac phonocardiographic observations of Soulié et al.[10] and our previous experience[15] agree with this conclusion.

Luisada and Testelli[11] and Liu and Jacono[12] recorded systolic and diastolic murmurs within the right atrium in cases of uncomplicated atrial septal defect. It was not possible to confirm these findings nor the other findings of Liu and Jacono[12] of duplication of the first sound within the pulmonary artery, fourth sound or presystolic murmurs within the pulmonary artery, and diastolic murmurs within the pulmonary artery. These authors used an entirely different technic for intracardiac phonocardiography[22] which consisted of using glucose solution within a regular catheter as the carrier of sounds to a pressure transducer situated outside the body.

In many reports on intracardiac phonocardiography in atrial septal defect[10–12, 15] accentuation of the first heart sound is not mentioned although this is considered a common feature on auscultation.[5, 23] The accentuation of the first heart sound on chest phonocardiography is due mainly to an increased intensity of the second main group of vibrations of the first heart sound.[5, 23] Simultaneous intracardiac and external phonocardiograms show that this loud first heart sound corresponds to the closure of the tricuspid valve.

SUMMARY

Thirty cases of atrial septal defect (20 of ostium secundum type, 4 of ostium primum type, 2 of Lutembacher's syndrome, 2 of persistent atrioventricular canal, and 2 of tricuspid atresia) were studied by means of an intracardiac microphone of activated barium titanate incorporated in the tip of a specially designed catheter.

In uncomplicated cases of atrial septal defect, the intracardiac phonocardiogram

demonstrated that both systolic and early diastolic murmurs heard at the base arose in the pulmonary artery, increased flow across the tricuspid valve was responsible for apical mid-diastolic and presystolic murmurs and the loud first sound was of tricuspid origin. No murmurs could be attributed to flow across the septal defect in either direction.

Among the cases of complicated atrial septal defect, the intracardiac phonocardiogram was of diagnostic help in cases of persistent atrioventricular canal by showing a pansystolic murmur in the outflow tract of the right ventricle, which suggested the presence of shunt at that level, and by showing a regurgitant murmur in the atrial chambers, which indicated incompetence of the atrioventricular valves. It was of diagnostic value in a case of Lutembacher's syndrome with atrial fibrillation, by revealing a mid-diastolic murmur within the inflow tract of the left ventricle in the absence of a pressure gradient across the mitral valve.

Acknowledgment

The authors are in debt to Drs. W. G. Bigelow, R. O. Heimbecker, and J. A. Key (University of Toronto), who carried out surgery and provided information about the anatomic type of atrial septal defect in the reported cases; to Dr. D. H. Lewis and J. D. Wallace (Philadelphia) who made available the necessary equipment, and to Drs. R. D. Rowe, R. W. Gunton, and C. R. Woolf (University of Toronto), for their advice in the preparation of the manuscript.

Summario in Interlingua

Trenta casos de defecto atrio-septal—20 de ostio secunde, 4 de ostio prime, 2 de syndrome de Lutembacher, 2 de persistente canal atrioventricular, 2 de atresia tricuspidic—esseva studiate per medio de un microphono intracardiac in le forma de un specialmente construite catheter con un puncta in que activate titanato de barium esseva incorporate.

In noncomplicate casos de defecto atrioseptal, le phonocardiogramma intracardiac demonstrava que le murmures tanto systolic como etiam eodiastolic que es audibile al base habeva lor origine in le arteria pulmonar, que le augmentate fluxo per le valvula tricuspidic esseva responsabile pro murmures apical mediodiastolic e presystolic, e que le forte prime sono esseva de origine tricuspidic. Nulle murmures poteva esser attribuite al fluxo per le defecto septal i le un o in le altere direction.

Inter le casos de complicate defectos atrioseptal, le phonocardiogramma intracardiac esseva de adjuta diagnostic in casos de persistentia del canal atrio-ventricular per demonstrar un murmure pansystolic in le via de effluxo del ventriculo dextere (lo que suggereva le presentia de un shunt a ille nivello) e per demonstrar un murmure de regurgitation in le cameras atrial (lo que indicava incompetentia del valvulas atrioventricular). Illo esseva de valor diagnostic in un caso de syndrome de Lutembacher con fibrillation atrial per revelar un murmure mediodiastolic intra le via de influxo del ventriculo sinistre in le absentia de un gradiente de tension trans le valvula mitral.

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The subject of the encouragement, or, as it is sometimes called, the endowment of research, has of late years greatly exercised the minds of men in England. Many seem to think that this question is mainly one of money; that you can go into the market and buy research, and that supply will follow demand, as in the ordinary course of commerce. This view does not commend itself to my mind. My own conviction is admirably summed up in the passage of your president's address, "that the best investigators are usually those who have also the responsibilities of instruction, gaining thus the incitement of colleagues, the encouragement of pupils, and the observation of the public."—Thomas H. Huxley. *American Addresses with a Lecture on the Study of Biology.* London, MacMillan and Co., 1877, p. 120.

Chronic Idiopathic Pericardial Effusion without Tamponade

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Persistent pericardial effusion in the absence of obvious preceding or concurrent disease presents a baffling problem. In such cases chylopericardium, cholesterol pericarditis, lupus erythematosus, malignant disease, myxedema, severe anemia, and scleroderma, must be considered. Six cases are reported with large effusions present for from 1 to 11 years. The diagnostic measures to be used, the results of histologic examination, and the effects of surgery on the clinical course are discussed.

PERICARDITIS with effusion is a relatively common form of acute pericardial inflammation that has been found in association with rheumatic fever,[1] serious infections of the respiratory tract with and without demonstrable etiologic agents,[2, 3] myocardial infarction,[4] and myocardial contusion.[5] In addition, pericardial effusion has been described in association with myxedema,[6–8] severe anemia,[9] tumors,[10] uremia,[11] and scleroderma,[12] and it is believed to occur at some time in more than 50 per cent of cases of systemic lupus erythematosus.[13] Chylopericardium[14] and cholesterol pericarditis[15–18] are rare entities. Rarely, pericardial effusion of considerable degree may follow a chronic course, usually with the late development of symptoms and signs of cardiac tamponade.[19–22]

The findings in 6 patients who had gross chronic pericardial effusion of unknown cause without the development of cardiac tamponade are described.

CASE REPORTS

Case 1

A 40-year-old white married woman had a hysterectomy at the Mayo Clinic in 1951 because of endometriosis. A thoracic roentgenogram did not reveal any abnormalities in the lungs or the cardiac shadow at that time.

At her second examination, in July 1952, she had many symptoms believed psychogenic in origin. Results of physical examination and laboratory studies revealed no abnormality other than in the thoracic roentgenogram, which disclosed moderate globular enlargement of the cardiac shadow (fig. 1 *a*). Specific questioning elicited a history of mild precordial distress on leaning forward, with occasional consciousness of the heart beat. Heart murmurs were not detected. The blood pressure was 110 mm. Hg systolic and 80 diastolic; the pulse rate was 80 beats per minute, with a regular rhythm. There was no clinical evidence of hypothyroidism. In view of the absence of objective signs of cardiac disease, treatment was not considered necessary but follow-up was advised.

The patient returned in November 1954, because of progressive enlargement of the cardiac shadow. She now complained of severe palpitation, tachycardia on exertion, and a dull lower substernal ache that extended toward the left axilla with inspiration. She had not noticed any significant exertional dyspnea, orthopnea, or peripheral edema. Neither digitalization nor a period of rest in bed for 3 months prior to this admission had produced any diminution in the size of the cardiac shadow.

Results of physical examination in 1954 were essentially unchanged as compared with those in 1952. However, roentgenologic studies revealed considerable increase in the size of the cardiac shadow (fig. 1 *b*). Hematologic studies gave normal results. Fluoroscopy showed slightly diminished cardiac pulsations. An electrocardiogram showed no significant abnormality. The venous pressure was 12 mm. Hg, corrected to the midlevel of the

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The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

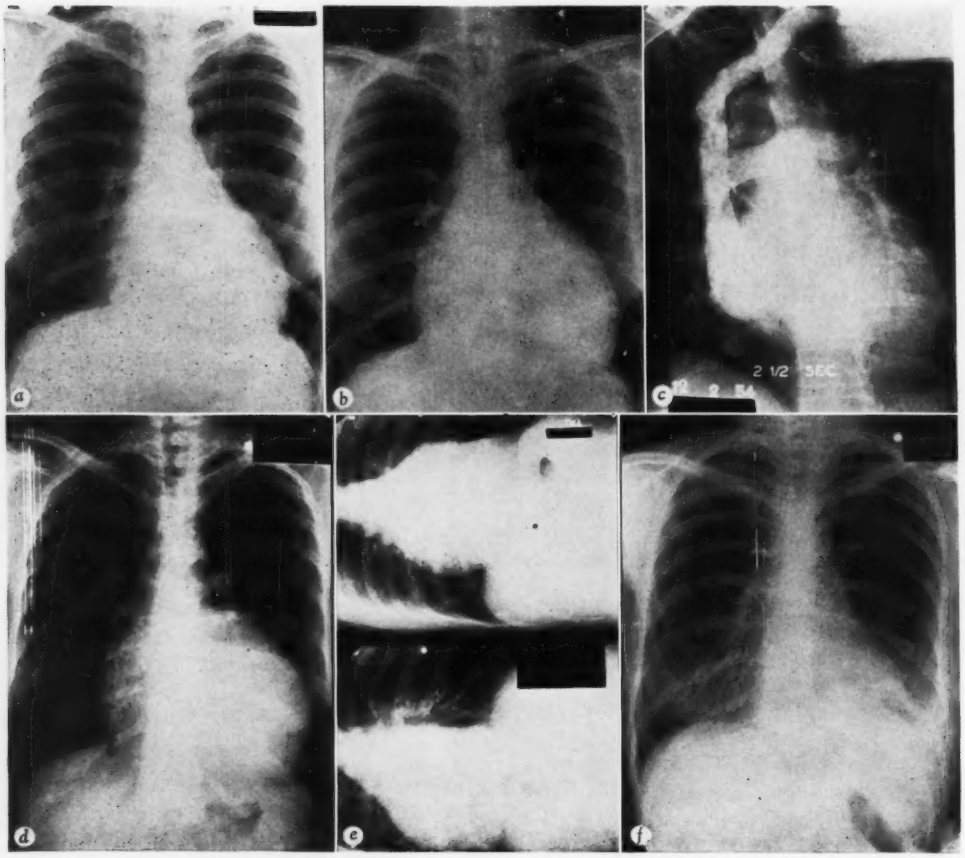

FIG. 1. Case 1. *a*. Enlargement of cardiac shadow in 1952. *b*. Further increase in size of cardiac shadow 2 years later. *c*. Angiocardiogram showing normal right atrial contour and demonstrating that enlargement of the cardiac shadow is caused by pericardial effusion or thickened pericardium. *d* and *e*. Roentgenograms taken in erect and lateral decubitus positions after removal of 80 ml. of pericardial fluid and replacement by air. *f*. Postoperative appearance, showing normal size of cardiac shadow.

right atrium. The presence of pericardial effusion was suspected, and angiocardiography demonstrated that the increased size of the cardiac shadow was not caused by enlargement of the cardiac chambers but was the result of pericardial effusion or thickening (fig. 1 *c*).

Diagnostic paracentesis, with removal of 80 ml. of clear yellow fluid and replacement by air, was performed prior to operation (fig. 1 *d* and *e*). More than 1,000 ml. of clear yellow fluid were removed at operation, and a large opening was made between the pericardium and the left pleural space. Cultures of the pericardial fluid did not produce any growth of *Mycobacterium tuberculosis*, brucellar organisms, fungi, or other pathogens. Histologic examination of the pericardium showed no abnormality. The size of the cardiac shadow became normal shortly after operation (fig. 1 *f*).

Comment. A large pericardial effusion was present in this patient for at least 2 years without the development of cardiac tamponade. No history of an episode suggesting acute pericarditis was obtained, and the cause of the effusion was not evident. Six months after operation, examination revealed no abnormality, and the size of the cardiac shadow was normal. The only postoperative change in the electrocardiogram was a moderate increase in the amplitude of the QRS complexes and T waves in most leads (fig. 2). This was the usual pattern in all 6 cases.

Case 2

A 42-year-old white married woman came for examination in January 1955. She had a history of chorea at the age of 15 years and of pulmonary embolism following a pelvic operation at age 28. Cardiac enlargement had been diagnosed in 1947 following mass miniature radiography, and progressive enlargement of the cardiac shadow had been observed in thoracic roentgenograms made at yearly intervals. She had taken digitalis continuously since 1948, when she complained of exertional dyspnea and fatigue.

The patient came to the clinic in January 1955 because of the progressive enlargement of the cardiac shadow. At this time, she complained of occasional pain in the anterior aspect of the thorax on the left side, with extension to the left shoulder and arm. She also complained of mild dyspnea on exertion, but she had not experienced orthopnea or paroxysmal nocturnal dyspnea.

Examination failed to reveal any cardiac murmurs, peripheral edema, or clinical evidence of increased venous pressure. The blood pressure and the cardiac rate and rhythm were normal. Hematologic studies gave normal results. Thoracic roentgenography showed considerable enlargement of the cardiac shadow, and this enlargement had increased steadily since 1947, judging by the yearly roentgenograms that were available (fig. 3 *a* and *b*). The electrocardiogram was interpreted as normal. The lupus erythematosus clot test on peripheral blood gave normal results. The value for plasma cholesterol was 169 mg. per 100 ml. The basal metabolic rate was 5 per cent, and she was clinically euthyroid.

The suspected presence of pericardial effusion was confirmed by angiocardiography (fig. 3 *c*). At operation, approximately 1,200 ml. of clear yellow fluid were removed from the pericardial sac. A "window" was made between the pericardium and left pleural space. Cultures of the pericardial fluid did not give growth of any pathogenic organisms. Biopsy of the pericardium gave normal results.

The patient was seen again in February 1956, at which time she was well. The cardiac shadow returned to normal size, and it was still normal in November 1957 (fig. 3 *d*).

Comment. Pericardial effusion was present in this patient for at least 8 years. Despite the history of chorea at age 15, evidence of rheumatic heart disease was absent, as was any evidence to suggest that the pericardial effusion was on a rheumatic basis.

Case 3

A 64-year-old white married woman came to the clinic in February 1955 because of a hard mass in the region of her thyroid gland.

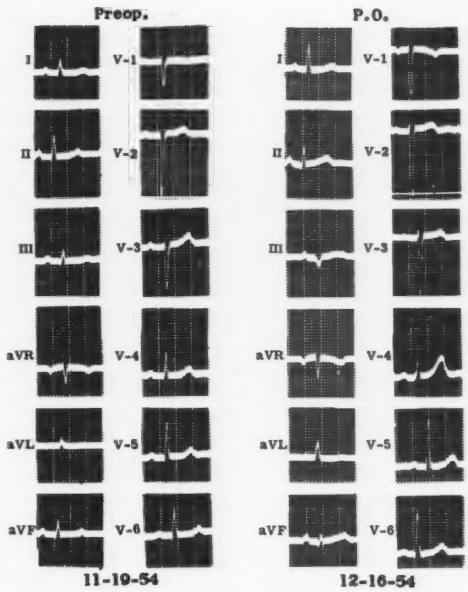

FIG. 2. Case 1. Preoperative and postoperative electrocardiograms. Note moderate increase in amplitude of QRS and T waves in most leads, without other significant changes.

She gave a history of exploration of her neck for substernal goiter in 1921, and partial removal of a thymic tumor (reported as a thymoma) in 1928. At the time of the latter operation, she had complained of dyspnea, and there was increased prominence of the superficial venous pattern over the neck and thorax that persisted after operation. Narrowing of the trachea also had been found in 1928. She had noted difficulty in taking a deep breath at that time but had not experienced orthopnea or paroxysmal nocturnal dyspnea. An "abnormal" thoracic roentgenogram had been noted in 1933, and she had been told of cardiac enlargement detected roentgenographically in 1953, although these films were not available for study. Subtotal hysterectomy had been done in 1945.

Examination in 1955 disclosed dilated superficial veins over the neck and upper part of the thorax. The thyroid gland was moderately enlarged, the left lobe being larger than the right, and a hard nodule was palpable in the right lobe. Cardiac murmurs were absent, and the cardiac rate and rhythm were normal. The blood pressure was 170/100, and mild hypertensive changes were present in the retinal vessels. Peripheral edema was absent, and exercise tolerance was normal for her age. The value for hemoglobin was 11.9

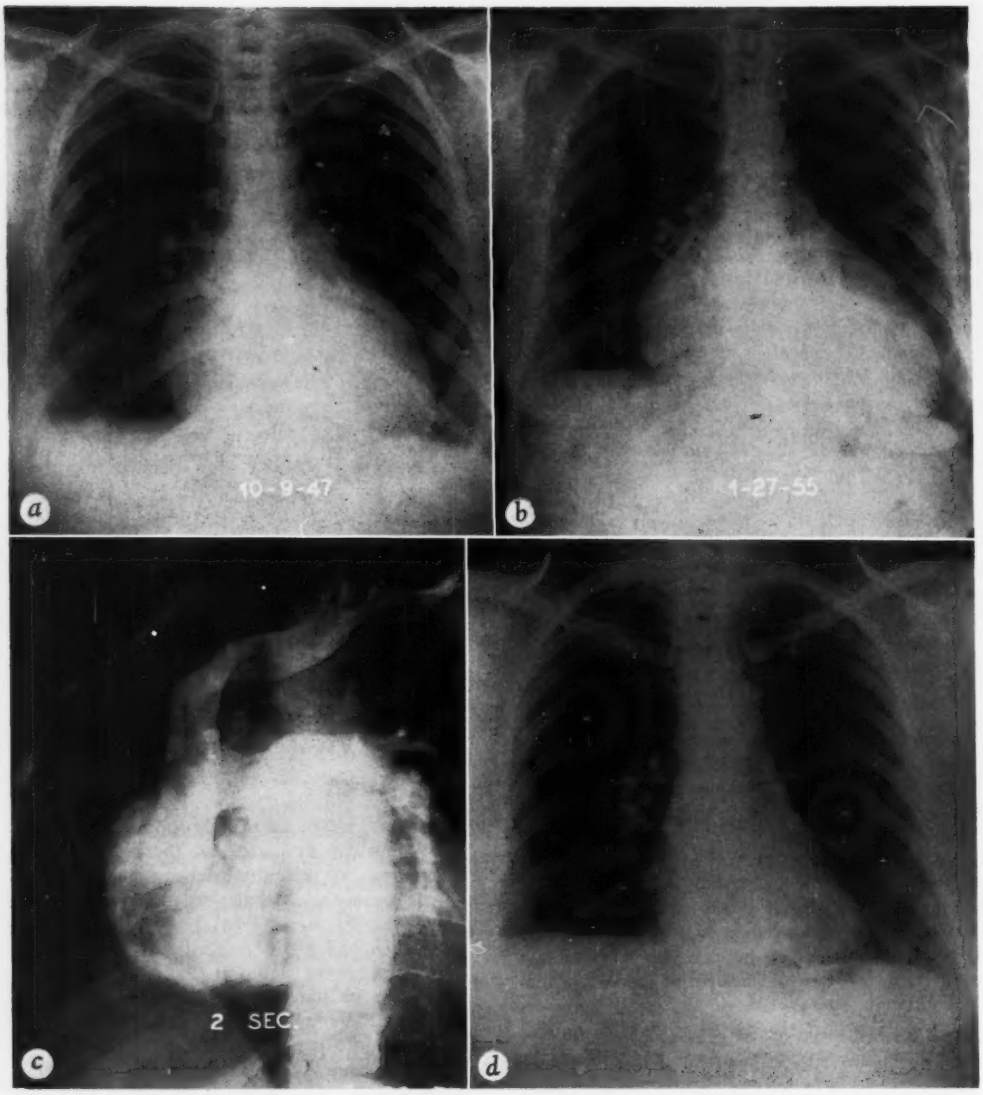

FIG. 3. Case 2. *a* and *b*. Note increase in size of cardiac shadow between 1947 and 1955. *c*. Angiocardiography demonstrates that the cardiac enlargement does not involve the cardiac chambers. *d*. Postoperative cardiac shadow of normal size.

Gm. per 100 ml. of blood; erythrocytes numbered 3,900,000 per mm.^{3} and the leukocyte count was 4,600. The erythrocytic sedimentation rate was 36 mm. during the first hour (Westergren technic). The thoracic roentgenogram showed globular enlargement of the cardiac shadow that was thought to indicate pericardial effusion (fig. 4 *a*). Other roentgenologic studies disclosed a calcified thyroidal adenoma on the right side and bilateral compression of the esophagus above the level of the clavicles. A partially calcified mediastinal mass also was present. The venous pressure was 20 mm. Hg in the arms and 19 mm. in the legs, corrected to the midlevel of the right atrium. The electrocardiogram showed decreased amplitude of the QRS complexes. Thyroidal uptake of radioiodine

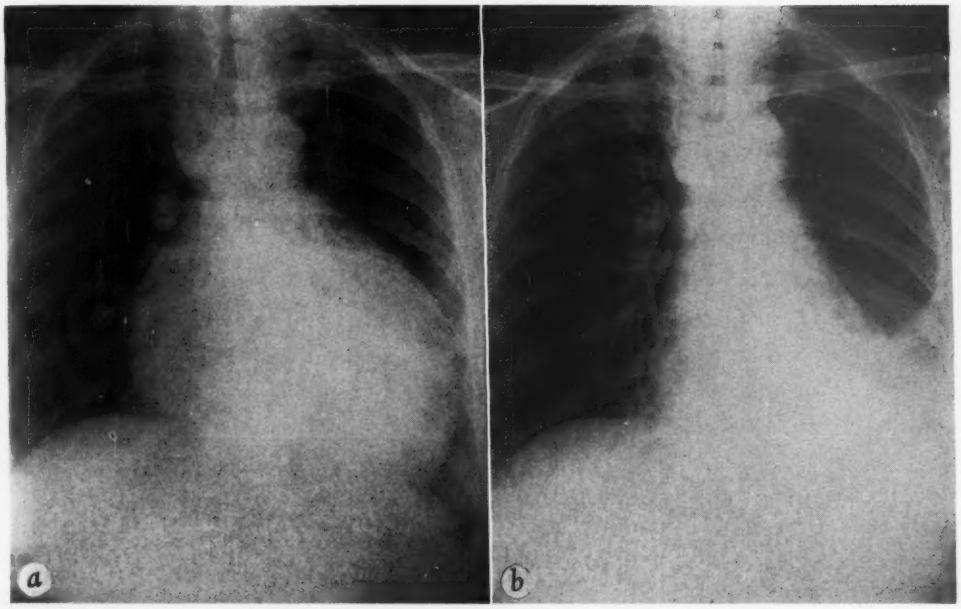

FIG. 4. Case 3. *a*. Note gross enlargement of cardiac shadow, together with an upper mediastinal shadow. *b*. Postoperative appearance, showing normal cardiac shadow.

was maximal in the region of the nodule in the right lobe. The value for protein-bound iodine was 5.8 μg. per 100 ml. of serum. Other laboratory studies were noncontributory. Angiocardiography was not attempted in view of the evidence of obstruction of the superior vena cava. The lesion in the thyroid gland was considered benign, and pericardial exploration was advised.

At operation, approximately 700 ml. of reddish-brown fluid were released from the pericardial sac. A diffuse calcified mass, thought to be scar tissue, was present in the mediastinum, involving the superior vena cava. There was no gross or microscopic evidence of recurrent thymoma. Malignant cells were not present in the fluid. Cultures of the pericardial fluid did not produce any growth of pathogenic organisms. Histologic examination of pericardial tissue revealed fibrous pericarditis with zones of infiltration by lymphocytes and plasma cells. Following operation, the patient stated that she could breathe more easily. The cardiac shadow became normal in size, although the evidence of superior vena caval obstruction was unchanged (fig. 4 *b*).

The patient was reexamined 9 months after operation, at which time she felt better and had no evidence of cardiac disease. The electrocardiogram showed some increase in amplitude of the QRS complexes as compared with the preoperative tracing. The evidence for superior vena caval obstruction remained, and the other findings were unchanged.

Comment. The chronicity of the effusion in this patient was assumed from the reported roentgenologic finding of cardiac enlargement 2 years before her initial examination at the clinic. Good historical evidence existed that superior vena caval obstruction had been present prior to the thoracotomy in 1928; at that time, a diagnosis of thymoma was made, and the tumor was partially removed, but the surgical record and tissue were not available. The thoracotomy in 1955 did not reveal evidence of recurrence of a thymic tumor, and examination of the pericardium and the pericardial fluid did not disclose malignant cells. It is thought justifiable to include this case as an example of chronic idiopathic pericardial effusion, although the possibility is recognized that the previous intrathoracic lesion and mediastinal scarring, with venous and lymphatic blockage, played an etiologic role.

Case 4

A 43-year-old white married woman came to the clinic in August 1955 because of loss of energy and weight. The menopause had occurred in 1954.

Examination disclosed a plethoric appearance. The blood pressure was 160/120. The retinal

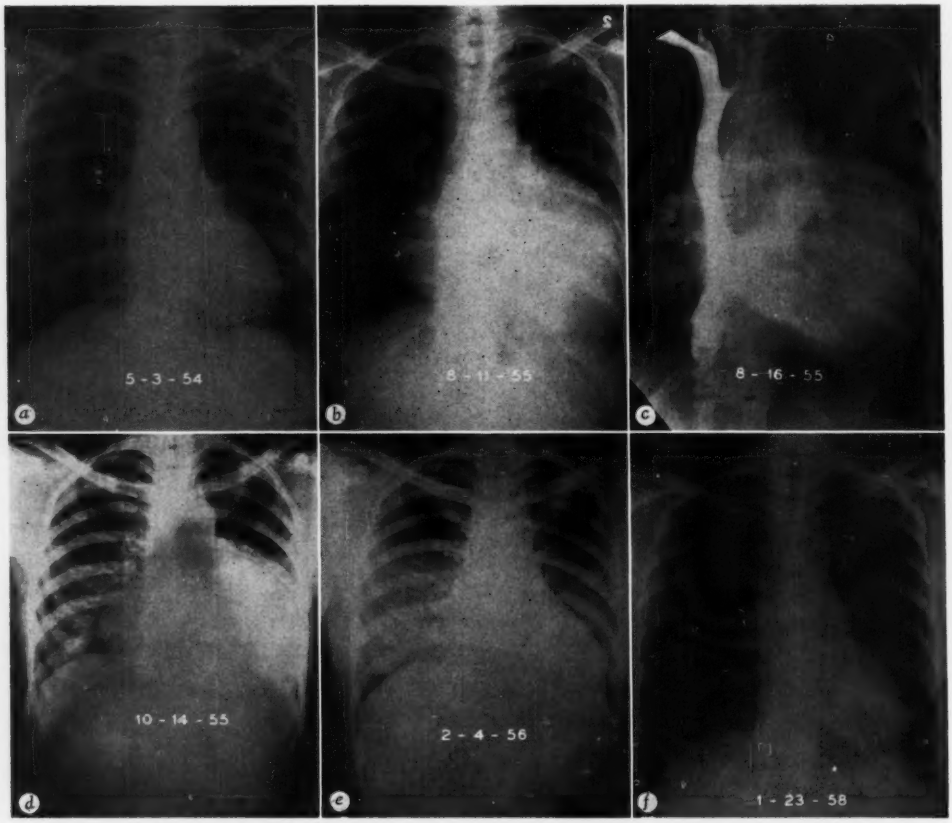

FIG. 5. Case 4. *a* and *b*. Note great increase in size of cardiac shadow over a period of 15 months. *c*. Angiocardiography demonstrates pericardial effusion with invagination of right atrium. *d-f*. Note spontaneous disappearance of effusion, with return of cardiac silhouette to normal.

arteries showed the changes of group 1 hypertension. The value for hemoglobin was 17.6 Gm. per cent, and the erythrocytes numbered 6,040,000 per mm.^{3} The volume of packed cells (hematocrit) was 62 per cent. Exercise tolerance was normal. Cardiac murmurs were absent, and the venous pressure was normal. A thoracic roentgenogram revealed pronounced increase in the size of the cardiac shadow as compared with a film taken in May 1954 (fig. 5 *a* and *b*). The cardiac pulsations were slightly diminished on fluoroscopy. The electrocardiogram showed a decreased QRS voltage, with inverted T waves in lead V_5. The presence of pericardial effusion was suspected, and angiocardiography substantiated this (fig. 5 *c*). The right atrium appeared to be slightly compressed by pericardial fluid or thickening. Results of tests of pulmonary function were normal. The possibility of a cardiac tumor was considered, and thoracotomy was advised.

The patient declined operation and returned home. In view of the polycythemia, she was advised to discontinue use of the cobalt-containing preparation of iron that she had been taking for several months for supposed anemia. Her home physician followed her progress with serial roentgenograms, which revealed diminution in size of her cardiac shadow, with a return to normal size by February 1956 (fig. 5 *d* and *e*). She was reexamined at the clinic in January 1958, at which time the roentgenogram (fig. 5 *f*) and blood counts were normal.

Comment. The subsequent clinical course of this patient appeared to eliminate the possibility of a pericardial tumor. It is possible that the polycythemia was caused by administration of the

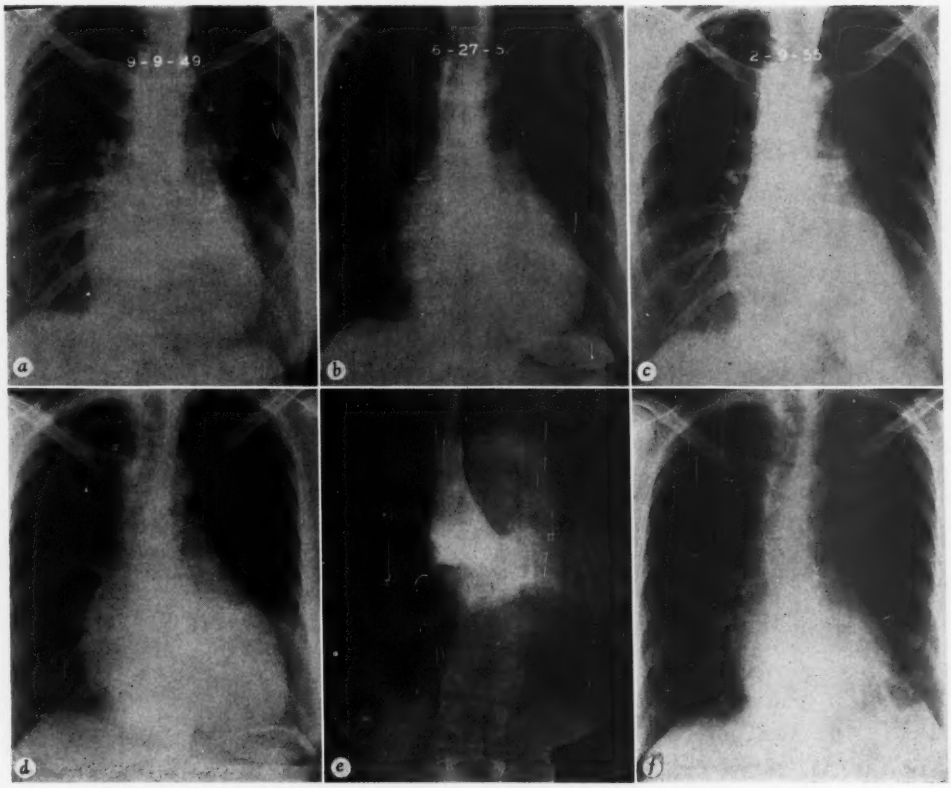

FIG. 6. Case 5. *a-d.* Note gradual increase in size of cardiac shadow between 1949 (*a*) and 1957 (*d*). *e.* Angiocardiography shows pericardial effusion. *f.* Postoperative return to normal cardiac shadow.

iron-cobalt preparation,[23] which also may have been a factor in the production of the pericardial effusion. Her blood counts were normal in February 1956, which was 7 months after she had discontinued use of the iron-cobalt preparation.

Case 5

A 54-year-old white woman came to the clinic in June 1957 because of concern over the gradual increase in cardiac size revealed by thoracic roentgenograms over a period of 11 years (fig. 6 *a-d*). Her chief complaint was chronic fatigue for many years. She did not give any history of exertional dyspnea, paroxysmal nocturnal dyspnea or orthopnea, and she had not been taking digitalis.

Examination did not reveal any significant abnormalities other than a retroverted uterus with small myomas. The blood pressure was 122/80. The heart sounds were normal, and there were no murmurs. Roentgenologic studies showed enlargement of the cardiac shadow, with normal pulmonary vascular markings (fig. 6 *d*). She appeared euthyroid, but she had been taking 0.5 gr. of desiccated thyroid daily for 11 years. Her history did not support the thesis that she had had myxedema. There was no evidence of pituitary insufficiency, although her menses had ceased at age 41 without the occurrence of hot flushes. The basal metabolic rate was —19 per cent, and the value for protein-bound iodine was 4.7 μg. The plasma cholesterol measured 190 mg. All other laboratory studies gave normal results. The venous pressure was 8 mm. Hg, corrected to the midlevel of the right atrium.

The patient was considered to be euthyroid, and pericardial effusion was thought to be the cause of the enlargement of her cardiac shadow. Angiocardiography confirmed this diagnosis (fig. 6 *e*).

At pericardial exploration, approximately 1,000 ml. of clear yellow fluid was removed from the pericardial sac. A "window" was made between

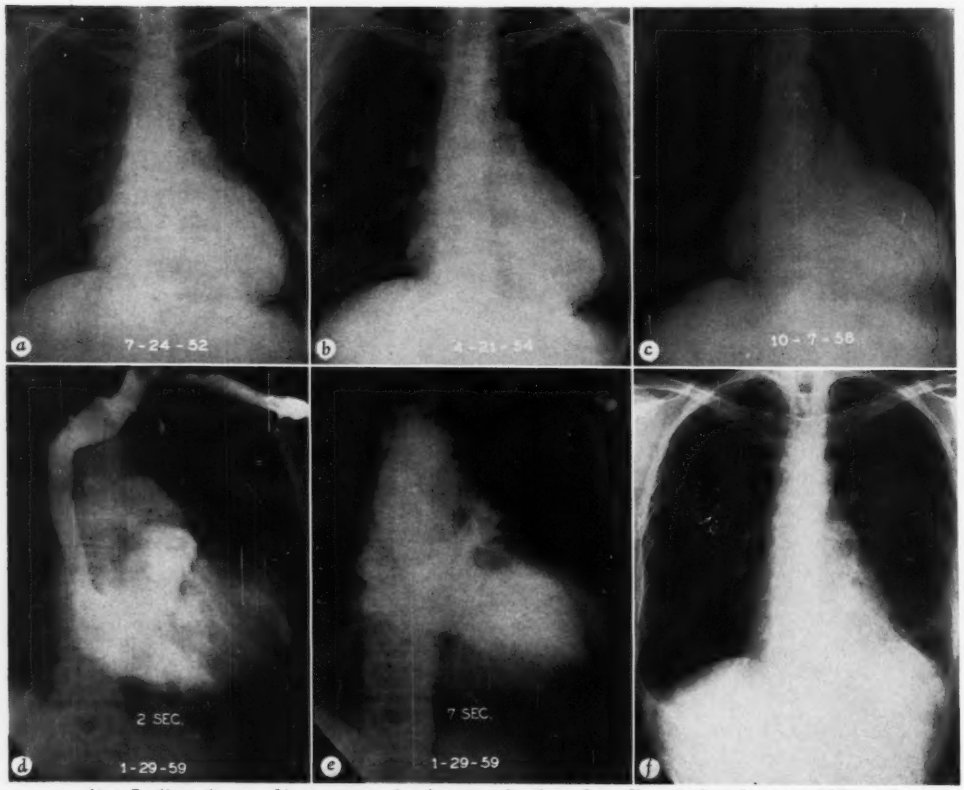

FIG. 7. Case 6. *a-c.* Note progressive increase in size of cardiac shadow between 1952 and 1958. *d* and *e.* Angiocardiography demonstrates pericardial effusion surrounding right and left cardiac chambers, respectively. *f.* Postoperative return of cardiac silhouette to normal.

the pericardium and the left pleura. Malignant cells were not found, and cultures of the fluid were negative for pathogenic organisms. The fluid did not contain any lupus erythematosus cells. Histologic examination of the pericardial tissue disclosed mild fibrous pericarditis. Postoperative roentgenograms showed the size of the cardiac shadow to be normal (fig. 6 *f*).

Case 6

A 52-year-old white married woman came to the clinic in October 1958. She was referred because of the roentgenologic finding of cardiac enlargement in 1952, with progressive increase in the size of the cardiac shadow since then (fig. 7 *a-c*). A thoracic roentgenogram in 1930 was alleged to have shown cardiac enlargement. She had not experienced exertional dyspnea or paroxysmal nocturnal dyspnea. She had had a mild degree of sternal depression since childhood. She complained of occasional aching pain in the left anterolateral aspect of the thorax that was not related to exertion. Hysterectomy and salpingo-oophorectomy had been done in 1948.

Examination disclosed normal heart sounds. The blood pressure was 140/70. The venous pressure was 7 mm. Hg, corrected to the midlevel of the right atrium. The retinal vessels were normal. Results of urinalysis and the values for blood sugar, blood urea, and plasma cholesterol were normal. The basal metabolic rate was +11 per cent. The value for protein-bound iodine was 4.7 μg. Results of the lupus erythematosus clot test on peripheral blood were normal. Considerable enlargement of the cardiac shadow was apparent on the thoracic roentgenogram; the pulmonary vascular shadows appeared normal (fig. 7 *c*). A slight funnel-chest deformity was present. The enlargement of the cardiac shadow was ascribed to pericardial effusion, and angiocardiography substantiated this impression (fig. 7 *d* and *e*).

Operation disclosed approximately 1,100 ml. of clear yellow fluid in the pericardial sac. A "window" was made between the pericardium and the

left pleural cavity. The fluid did not contain malignant cells or lupus erythematosus cells. Cultures failed to disclose any pathogens. Histologic study of the pericardial tissue showed practically normal pericardium apart from a mild increase in fibrous tissue. A postoperative roentgenogram showed the cardiac shadow to be normal (fig. 7 *f*).

Comment. Enlargement of the cardiac shadow in this patient had been evident roentgenologically since 1952. A roentgenogram in 1930 was reported to have shown cardiac enlargement, but this film was not available for examination. There has been no long-term follow-up on this patient, since the operation was done in February 1959.

Discussion

Three cases of chronic pericarditis with effusion were reported by Barker and Johnston.[19] The effusion in their 3 male patients persisted from 7 months to 4 years. There was no evidence of tuberculosis or rheumatic disease, but a possible etiologic factor was present in 2 of the patients in the form of previous pneumonia and injury to the thorax, respectively. Two of the patients presented evidence of constrictive pericarditis after the effusion had lasted 4 and 2 years, respectively; a case somewhat similar to these 2 of Barker and Johnston has been reported by one of us.[22]

Soloff and Bello[9] reported 2 cases of pericardial effusion in association with severe anemia; the effusion had been present for at least 4 years in one case. Contro and co-workers[24] reported chronic symptomless pericardial effusion lasting 4 years after pneumonia occurring at the age of 7 years. Guidotti and Puddu[25] reported 2 cases of chronic pericardial effusion in 2 patients, a 46-year-old man and a 39-year-old woman, who were otherwise in apparently good health.

Genecin[26] recently described chronic pericardial effusion in 2 brothers. Polycythemia was present in the younger patient and the effusion had the characteristics of "cholesterol pericarditis." A vascular anomaly of the skin and eyegrounds was noted in the older patient.

All of our 6 patients were women, and 5 were menopausal. There was no evidence of active tuberculosis or rheumatic disease at the time of examination, and none had myxedema or signs of systemic lupus erythematosus. Evidence of cardiac tamponade was not present in any of these patients, but the venous pressure was grossly increased in 1 (case 3) because of superior vena caval obstruction some 25 years previously. The duration of the pericardial effusion ranged from 1 to 11 years; fluid may have been present as long as 29 years in case 6, although the reported "cardiac enlargement" in 1930 in this instance could not be verified. In case 3, the chronicity of the effusion was assumed from the reported roentgenologic findings of cardiac enlargement at another institution 2 years before. In case 4, the pericardial effusion was possibly present for only a short period before the initial abnormal roentgenogram (fig. 5). None of the 6 patients gave a history suggesting an episode of acute pericarditis. Examination of the pericardial fluid gave no clue to the etiologic factor, and histologic study of pericardial tissue was uniformly nonrevealing. Case 4 is of interest in view of the coincidence of pericardial effusion and polycythemia, which almost certainly was induced by ingestion of a cobalt-containing preparation of iron.

The diagnosis of pericardial effusion has been made during cardiac catheterization by demonstrating that the tip of the catheter touched the lateral wall of the right atrium but did not reach the limit of the cardiac shadow.[27] Pericardial effusion also has been diagnosed by the characteristic configuration of the right ventricular pressure pulse, with its early diastolic dip and the increased end-diastolic pressure.[28] However, it appears that this diagnostic configuration of the right ventricular pressure pulse is the result of restriction of diastolic relaxation of the ventricles, and it should not be found in patients with pericardial effusion in whom cardiac constriction has not occurred.[29, 30]

The value of angiocardiography as an aid to the diagnosis of pericardial effusion has been described previously[31, 32] and is again demonstrated in our 6 patients. Carbon dioxide also has been used as a contrast medium to demonstrate the extraluminal density produced by pericardial effusion.[33, 34] The obtaining of fluid by pericardial puncture estab-

lishes the diagnosis, and replacement of the fluid by air gives information as to cardiac size and the degree of thickening of the parietal pericardium, as well as showing the limits of pericardial reflection on the great vessels. Clinical examination, fluoroscopy, and electrocardiography were not of significant discriminatory value in our cases. The lack of evidence of a lesion capable of producing cardiac hypertrophy or dilatation served as a clue to the possible existence of pericardial effusion, and this also should be considered when thoracic roentgenography shows an enlarged cardiac shadow without abnormality of the pulmonary vascular shadows.

It is appreciated that pericardial effusion may represent a stage in the development of chronic constrictive pericarditis. It is remarkable that none of these 6 patients gave any evidence of constriction after persistence of the effusion for periods up to 11 years.

None of our patients exhibited the prominent third heart sound in early diastole described by Barker and Johnston in 2 of their cases and occurring commonly in chronic constrictive pericarditis. This sound is related to the early decrease in diastolic pressure in the ventricular pulse of patients who have cardiac constriction;[13] this mechanism is not present in pericardial effusion unless the fluid is under sufficient pressure to cause restriction of diastolic relaxation of the ventricles.[30]

Angiocardiography revealed some invagination of the right atrium in 1 patient (case 4), but there was no evidence of a large organized thrombus in the right atrium, such as was found in 2 of the cases of Barker and Johnston.

The operation performed on 4 of our patients, namely creation of a "pleuropericardial window," previously has been found satisfactory in patients with pericardial effusion.[20, 21]

Follow-up for variable periods has not revealed any evidence of recurrence of pericardial effusion in these 6 patients, all of whom noted subjective improvement.

Summary

Six cases of chronic pericardial effusion of unknown cause are reported. The effusion in 1 patient followed an old thoracotomy and evidence of obstruction of the superior vena cava. The remaining 5 patients had not experienced any significant preceding illnesses, operations, or trauma. The appearance of the pericardial effusion in 1 patient appeared to be coincident with the onset of polycythemia, and disappearance of the effusion followed correction of the polycythemia.

No evidence of cardiac tamponade was found in any of the patients despite the persistence of effusion for periods up to 11 years. In 5 of the patients, the pericardial fluid measured from 700 to 1,200 ml. at the time of operation.

The importance of angiocardiography as an aid to the diagnosis of pericardial effusion again is emphasized.

Summario in Interlingua

Es reportate 6 casos de chronic effusion pericardial de etiologia obscur. In 1 del patientes, le effusion sequeva un ancian thoracotomia e indicios de obstruction del vena cave superior. Le altere 5 patientes habeva experientiate nulle previe morbo, operation, o trauma de signification. Le apparition del effusion pericardial in 1 patiente coincideva apparentemente con le declaration de polycythemia. Correction del polycythemia esseva sequite per disparition del effusion.

Nulle indicios de tamponage cardiac esseva constatate in ulle del casos, in despecto del persistentia del effusion durante periodos de usque a 11 annos. In 5 del patientes, le liquido pericardial amontava a inter 700 e 1.200 ml al tempore del operation.

Le importantia de angiocardiographia como adjuta in le diagnose de effusion pericardial es sublineate de novo.

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Abnormalities of the Arterial Pulse Wave in Young Diabetic Subjects

By Henry Lax, M.D., and Arthur W. Feinberg, M.D.

With the technical assistance of William Urban

Abnormalities have been noted in the arterial pulse wave of human subjects with peripheral arteriosclerosis and with hypertension. The major change, diminution to disappearance of the dicrotic wave, has also been found in young diabetic subjects. The present study reports on the differences in the configuration of the arterial pulse wave of 162 diabetic subjects between the ages of 11 and 29 years and a comparable group of 275 nondiabetic controls. The findings seem to support the concept that the vascular abnormalities seen in diabetes mellitus are an integral part and not a complication of the disease.

THE increased tendency of the diabetic patient to develop evidences of vascular degeneration has been well documented. White,[1] Dolger,[2] and others[3, 4] have shown that almost all diabetic subjects have clinically apparent vascular lesions by the time they have had the disease for 15 years. The work of Mendlowitz and associates[5] and of Megibow et al.[6] with young adult diabetic persons suggests that there may be vascular impairment in this disease before such changes can be recognized clinically. Ditzel and Sagild[7, 8] have described abnormalities of the capillaries of the bulbar conjunctiva in diabetic subjects as young as 4 years of age and in a few nondiabetic adults with a positive family history of the disease. To our knowledge, there have been no other reports of vascular impairment in diabetic children.

Previous studies[9] have shown abnormal configurations of the arterial pulse wave in a high proportion of diabetic adults. This report is a comparison between the appearance of the arterial pulse wave in diabetic children and young adults up to the age of 30 years and in a comparable group of nondiabetic controls.

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A preliminary report of this investigation was presented at the October 1958 meeting of the American Heart Association, San Francisco, Calif.

Methods and Materials

A new recording technic has been utilized to obtain accurate, reproducible tracings of the arterial pulse wave without resorting to intraarterial puncture. The method involves the application of a sensitive rubber cuff with an inelastic backing about the finger to be tested. Arterial pulsations are picked up from the digit and transmitted by a system of tubing to a piezo-electric crystal. The pressure changes in the cuff, due to arterial pulsations, are transformed into changes in electrical potential, which are then amplified, actuate a string type mirror galvanometer, and are recorded photographically.[9, 10]

The technic has been shown to be sensitive and to give reproducible results. The accuracy of the recordings has been demonstrated by the similarity of simultaneous intraarterial and periarterial tracings.[9]

Figures 1 and 2 show typical examples of normal and abnormal pulse waves as recorded by this technic. The change in the abnormal cases appears to be diminution to disappearance of the dicrotic wave. This change in the configuration of the dicrotic wave has previously been found in patients with arteriosclerosis, with hypertension, and in all adult diabetic patients over the age of 40 years.[9]

One hundred and sixty-two diabetic patients between the ages of 11 and 29 years were examined at either the Vanderbilt Clinic of the Columbia-Presbyterian Medical Center or Camp

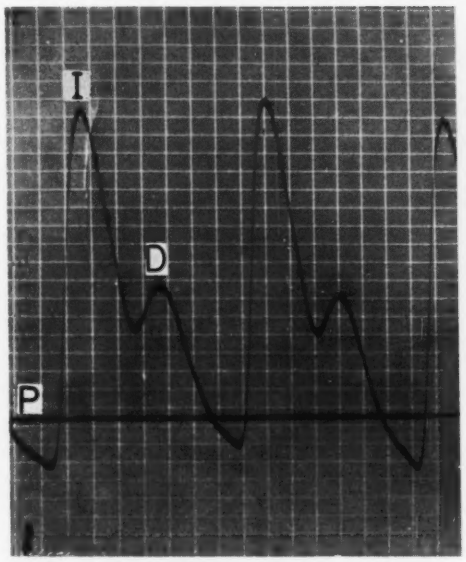

FIG. 1. Normal arterial pulse waves recorded from the third digit of a healthy 25-year-old man. *Vertical lines*, time signals 0.1 second apart; *horizontal lines*, pressure increments of 10 mm. Hg in the cuff applied about the finger. The cuff pressure (*P*) is recorded simultaneously but independently of the components of the pulse wave. Note the initial wave (*I*) and the well-defined dicrotic wave (*D*).

NYDA, a summer camp for diabetic children sponsored by the New York Diabetic Association. All of these patients took insulin. None exhibited any evidence of arteriosclerosis or hypertension on careful physical examinations. Chest x-rays were normal, as was palpation of the peripheral blood vessels. Retinal vessels were examined independently by a group of ophthalmologists and adjudged normal.

Two hundred and seventy-five presumably normal control subjects between the ages of 11 and 29 years were also examined with this technic. Most of the children between 11 and 16 years of age were at the Pleasantville Cottage Camp for Children just outside New York City. None of the control subjects exhibited glycosuria and those with a family history of diabetes were not included in this section of the study.

RESULTS

Ninety-nine (62 per cent) of the 162 diabetic subjects had abnormal arterial pulse waves, as shown by a diminution to disappearance of the dicrotic wave. In contrast, only 22 (8 per cent) of the 275 presumably healthy young people, also between the ages of 11 and 29 years, had abnormalities of their arterial pulse wave recordings.

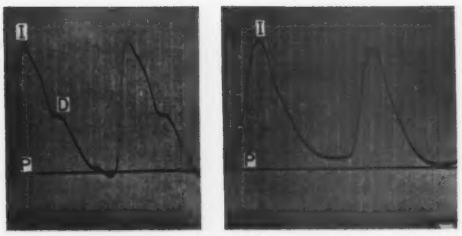

FIG. 2. An abnormal arterial pulse wave is shown, *left*. Note the diminished size of the dicrotic wave (*D*). A more severely abnormal arterial pulse wave is shown, *right*, with a complete absence of the dicrotic wave. The cuff pressure (*P*) is recorded on both tracings.

Subdivision of the diabetic and control groups by age did not alter the results (fig. 3). There were 203 normal children between the ages of 11 and 20 of whom only 7 per cent displayed any abnormalities, whereas 60 per cent of 134 diabetic children of comparable age had diminished to absent dicrotic waves. There were 72 normal subjects between the ages of 21 and 30 years, of whom only 11 per cent showed any abnormalities while 68 per cent of 28 diabetic subjects in this decade had abnormal arterial pulse waves.

No correlation could be established between the severity of the diabetes, as measured by insulin requirements, and the presence of an abnormal arterial pulse tracing. The longer the duration of diabetes, however, the more likely was the pulse wave to be abnormal (table 1). About half of 85 subjects who had been diabetic less than 5 years had abnormal arterial pulse waves. Seventy-six per cent, however, were abnormal among 77 persons who had been diabetic longer than 5 years. None of these patients, it is important to emphasize, had any clinical evidence of vascular disease.

In some cases more than one child from the same family was studied. Figure 4 reproduces the recordings from the index

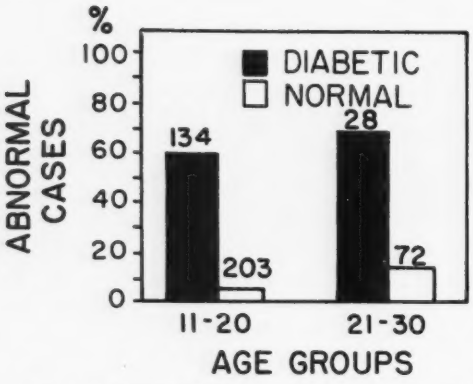

FIG. 3. The percentage of cases with an abnormal arterial pulse wave in the 2 age groups studied.

fingers of 3 siblings, ages 11, 14, and 15. The tracing with the diminished dicrotic waves is that of a 15-year-old boy who had known diabetes for 6 years. Neither of his siblings is diabetic and both have well-defined dicrotic waves.

Forty normal subjects between 11 and 29 years of age, who gave a positive family history of diabetes, were also studied. Although none showed evidence of vascular disease, 30 per cent had abnormal arterial pulse wave recordings as compared to 8 per cent abnormalities among 275 control subjects without a positive family history of diabetes (fig. 5). Glucose tolerance tests were not performed.

DISCUSSION

The high incidence of arteriosclerotic changes in patients with diabetes mellitus is well known and, until recently, has been considered to be a complication of the carbohydrate derangements in the disease. Dolger[2] first suggested that the circulatory and metabolic aspects may well be independent of one another and that vascular impairment may be a basic manifestation rather than a complication of diabetes. Support for this newer concept has been reported in the past few years. Mendlowitz[5] performed calorimetric studies and demonstrated decreased digital blood flow in the toes of young diabetic adults that was independent of the

TABLE 1.—*Effect of Duration of Diabetes on Occurrence of Abnormal Arterial Pulse Wave Recordings*

No. of subjects	Duration of diabetes ↓	Vasculogram Normal	Vasculogram Abnormal
85	<5 Years	42(49%)	43(51%)
77	>5 Years	20(24%)	57(76%)

severity, duration, or age of onset of their disease. Megibow[6] reported evidences of peripheral vascular impairment in adult diabetic subjects, who had no clinical evidence of arteriosclerosis, by employing a microplethysmographic technic. Wagener[11] has reported retinopathy in patients whose only manifestation of diabetes was a positive glucose tolerance test. Ditzel and Sagild[7, 8] have demonstrated changes in the capillaries and venules of the bulbar conjunctiva of normotensive diabetic subjects as young as 4 years of age, none of whom showed any other evidence of vascular disease. They also reported that of 6 supposedly nondiabetic adults who showed marked abnormalities of their capillaries, 4 had diabetes in their immediate family history.

Our results lend additional support to the concept that diabetes mellitus is, in actuality, a multifaceted disease process. The pulse wave alterations are present early in the course of the disease and are already found in half of the children studied when diabetes had been present less than 5 years. An even higher proportion of abnormal cases is found as the duration of the disease lengthens. No correlation could be established between the presence of this abnormality and the severity of the diabetes, as measured by insulin requirements. It is important to emphasize that all of these patients had severe enough diabetes to require insulin. None had any clinical stigmata of vascular disease.

Further evidence that the vascular abnormalities are not a consequence of the disturbed carbohydrate metabolism is the fact that a high percentage of normal children with a positive family history of diabetes show alterations of their arterial pulse waves.

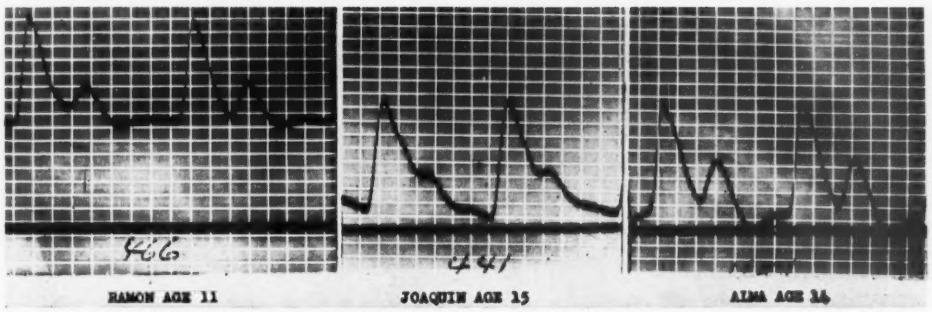

FIG. 4. Arterial pulse wave recordings from the index fingers of three siblings. The center tracing is from a 15-year-old boy with diabetes and shows a markedly diminished dicrotic wave when compared to his nondiabetic brother and sister.

Thirty per cent of the patients with a positive family history had abnormal dicrotic waves as compared to only 8 per cent abnormalities in the control group.

A major drawback to clinical studies in this field has been the lack of simple methods of examining the vascular system. Physical examination rarely shows evidence of vascular abnormalities in diabetic children. Microplethysmographic and calorimètric examinations require careful controls of room and extremity temperature and are impractical for large-scale studies. The technic described here has the advantage of being simple to use and of giving accurate, reproducible recordings of the arterial pulse wave without requiring intra-arterial puncture.

The mechanism of the observed change in the dicrotic wave is still not clear. Classically, the dicrotic wave has been ascribed to rebound against the closed aortic valve. More recent studies[12, 13] have indicated that peripheral factors play an important role in the formation of the dicrotic segment of the arterial pulse wave. Our recent study[10] of the different effects produced by epinephrine and norepinephrine on the dicrotic wave, further supports the concept that the dicrotic wave is predominantly of peripheral origin.

Whether the altered dicrotic wave found in young diabetic patients reflects some change in elasticity or whether it represents true organic change in the blood vessels of these people is undetermined. Whatever the

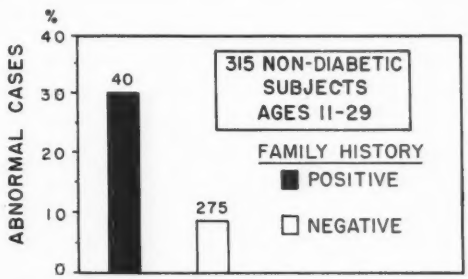

FIG. 5. Higher incidence of abnormal arterial pulse waves in nondiabetic subjects with a family history of diabetes as compared to a control group with a negative family history of diabetes.

cause, a method has been presented that seems to offer a means of detecting changes in the configuration of the arterial pulse wave of young diabetic patients, and in some nondiabetic subjects with a family history of the disease, that antedates clinical evidences of change in their vascular system.

SUMMARY

A simple, accurate reproducible technic for recording the arterial pulse wave without requiring intra-arterial puncture has been used to study 162 diabetic subjects between the ages of 11 and 29 years and a similar group of 275 nondiabetic controls. Sixty-two per cent of the 162 diabetic subjects had abnormal arterial pulse waves. The change noted was diminution to disappearance of the dicrotic wave. None had any clinical evidences of vascular disease. Only 8 per cent

of 275 nondiabetic control subjects of the same age group had abnormal configurations of the arterial pulse wave.

Forty-nine per cent of the diabetic patients who had the disease less than 5 years had abnormal pulse waves; 76 per cent were abnormal in the group who had been diabetic longer than 5 years. Although apparently nondiabetic themselves, 30 per cent of 40 patients with a positive family history of diabetes had abnormal arterial pulse waves.

These findings seem to support the concept that the vascular abnormalities seen in diabetes mellitus are an integral part and not a complication of the disease.

ACKNOWLEDGMENT

We would like to express our appreciation to the New York Diabetes Association and to the Director and staff of Camp NYDA and of the Pleasantville Cottage Camp for Children for their whole-hearted cooperation in every phase of this study.

SUMMARIO IN INTERLINGUA

Un simple, accurate, e reproducibile technica pro le registration del unda de pulso arterial, non requirente punctura intra-arterial, esseva usate in le studio de 162 subjectos diabetic de etates de inter 11 e 29 annos e de un simile gruppo de 275 nondiabetic subjectos de controlo. Sexanta-duo pro cento del 162 subjectos diabetic habeva anormal undas de pulso arterial. Le tracto notate como characteristic esseva diminution o mesmo disparition del unda dicrotic. Nulle subjecto in iste gruppo exhibiva signos clinic de morbo vascular. Solmente 8 pro cento del nondiabetic subjectos de controlo del mesme gruppos de etate habeva configurationes anormal in lor undas de pulso arterial.

Inter le diabeticos in qui le morbo habeva un duration de minus que 5 annos, 49 pro cento habeva anormal undas de pulso arterial. Inter le diabeticos in qui le morbo habeva un duration de plus que 5 annos, 76 pro cento habeva anormal undas de pulso arterial. In un gruppo de 40 patientes nondiabetic sed con un historia familial de diabete, 30 pro cento habeva anormal undas de pulso arterial.

Iste constatationes pare supportar le conception que le anormalitates vascular que es incontrate in diabete mellite es un parte integral del morbo e non un complication de illo.

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By D. W. Richardson, M.D., E. M. Wyso, M.D., A. M. Hecht, M.D., and D. P. Fitzpatrick, M.D.

In order to test photoelectric recording of dye curves, simultaneous determinations of cardiac output were made in 48 patients with heart disease with the Fick and dye-dilution technics. The dye curves were recorded with a Colson densitometer following either intrathoracic or antecubital injection of dye. Both Evans blue and indocyanine green dyes were employed. Satisfactory agreement was noted between Fick and dye estimates, demonstrating empirically the usefulness of the continuous recording technic.

AVAILABILITY of a cuvette densitometer,[1] allowing continuous recording of the concentration of Evans blue dye in the blood, has simplified methodology for estimation of cardiac output by the dye-dilution technic. The classic Hamilton dye-dilution method with intermittent sampling and measurement of dye concentration in plasma has been repeatedly shown to compare closely with the Fick technic for measurement of cardiac output in normal human subjects,[2, 3] and in patients with heart disease,[4–6] but photoelectric recording of changing dye concentration in whole blood has been criticized, particularly because of the variable optical properties of flowing blood.[7] The present study was undertaken to compare estimates of cardiac output obtained by the Fick and dye-dilution technics, the latter utilizing a densitometer that continuously recorded the concentration of dye in whole blood. Comparisons were also made between intrathoracic and arm-vein injection of dye.

Methods

Subjects were 48 hospital patients with cardiovascular disease ranging in age from 25 to 72 years and in functional classification from I to III. None was dyspneic at rest at the time of catheterization. No premedication was given; procaine 1 per cent was used at the sites of phlebotomy and of the intra-arterial needle. All subjects breathed room air.

In a typical experiment the catheter was introduced into the pulmonary artery and a needle was inserted into a brachial artery. Blood samples for calibration of the densitometer were withdrawn from the brachial artery. A 15-minute rest period was then allowed, following which cardiac output measurements were performed. When possible, a Fick determination and a dye curve were followed by another Fick determination and dye curve, performed as rapidly as was possible, usually within 30 minutes.

Dye was injected through a calibrated syringe-needle or syringe-catheter system. For recording dye-dilution curves, blood was drawn from the brachial artery through a Cournand needle, a polyethylene tube 4 inches in length with inside diameter of 0.75 mm. (Clay-Adams PE 60), and through the cuvette of a standard Colson Model-103 densitometer. The volume between the tip of the arterial needle and the outflow from the cuvette was 0.9 ml. The internal volume of the cuvette was 0.04 ml. Blood was drawn through the cuvette at rates of 0.6 to 0.8 ml. per second. The Colson densitometer[8, 9] consists of (1) an incandescent bulb light source; (2) Bausch-Lomb interference filters for selection of light with wavelength of 630 mμ., the maximum absorption wavelength of Evans blue, or of 800 mμ., the peak absorption wavelength of indocyanine-green dye; (3) a cuvette through which blood passes, made of 2 plane glass surfaces 1.0 mm. apart, with exposure of a channel ⅛ by ½ inches through which light passes from light source to photomultiplier; and (4) a photomultiplier (RCA 931A) with associated electronic circuitry to provide output voltage linearly proportional to optical density of solutions in the cuvette.

Two different calibration systems were used in

From the Medical Service, Veterans Administration Hospital, and the Department of Medicine, Medical College of Virginia, Richmond, Va.

of 275 nondiabetic control subjects of the same age group had abnormal configurations of the arterial pulse wave.

Forty-nine per cent of the diabetic patients who had the disease less than 5 years had abnormal pulse waves; 76 per cent were abnormal in the group who had been diabetic longer than 5 years. Although apparently nondiabetic themselves, 30 per cent of 40 patients with a positive family history of diabetes had abnormal arterial pulse waves.

These findings seem to support the concept that the vascular abnormalities seen in diabetes mellitus are an integral part and not a complication of the disease.

ACKNOWLEDGMENT

We would like to express our appreciation to the New York Diabetes Association and to the Director and staff of Camp NYDA and of the Pleasantville Cottage Camp for Children for their whole-hearted cooperation in every phase of this study.

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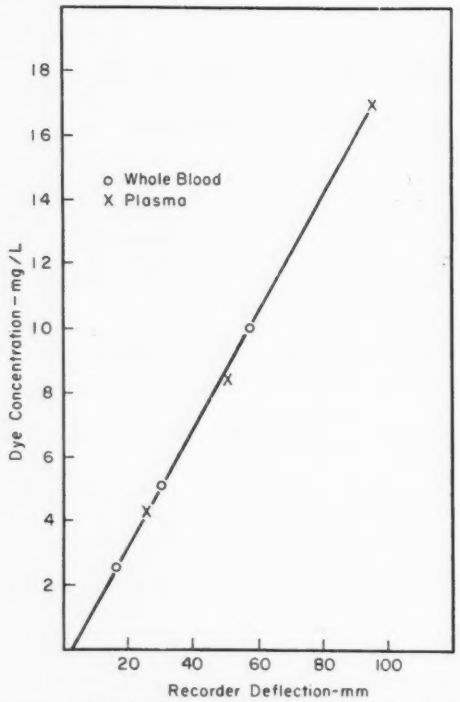


FIG. 1. Relation between dye concentration and deflection of the densitometer recorder system. Indocyanine-green dye was dissolved in whole bank blood to make 3 known dye concentrations. Each sample was drawn through the cuvette and its effect on densitometer deflection was recorded. The samples were then centrifuged and their plasma pulled through the cuvette. The graph demonstrates the linear relation between dye concentration and recorder deflection in plasma and in whole blood. Similar linearity was found with Evans blue dye.

the studies reported. All results regarding measurements of cardiac output using Evans blue dye were derived from curves calibrated as follows: prior to the measurement of cardiac output in each patient 100 ml. of arterial blood were collected anaerobically in a mercury-filled sampling tube. Twenty-milliliter lots of this undyed blood were transferred anaerobically to oiled syringes, and a known volume of 5 per cent Evans blue dye was then added from a calibrated Krogh-Keys pipette through a long, no.-26 needle into each syringe. For each patient, these anaerobically prepared samples, one of which was undyed and 3 of which contained varying concentrations of dye, were then pulled through the same needle, tubing, and cuvette, with use of the same falling-mercury sampling system. Rate of blood flow through the cuvette was, therefore, the same during calibration as during recording of the dye curves. From these anaerobically collected blood samples a graph of the relation between dye concentration and recorder deflection was plotted. From this relation a factor was derived that was used to convert millimeters of recorder deflection to concentration of dye.

In the studies using indocyanine-green dye,[10] a syringe pump capable of drawing blood through the Colson cuvette at a constant rate was employed, and measurements made with green dye were calibrated according to a method described by Theilen et al.[11] similar to that used by Emmanuel, Lacy, and Newman.[12]

Figure 1 demonstrates the linear relation between deflection of the cuvette-recorder system and concentration of indocyanine-green dye in both plasma and whole blood. Similar linearity was observed with Evans blue dye.

Fick gas collections were made over 5- or 6-minute periods with use of a nose clip, mouthpiece, and Douglas bag. Arterial and mixed venous samples were collected anaerobically over a 1-minute period in the middle of the gas collection. Blood samples were analyzed in duplicate for oxygen by the technic of Van Slyke and Neill,[13] expired gas was analyzed for carbon dioxide and oxygen by the Scholander apparatus, and oxygen consumption was calculated by the method of Haldane and Priestly.[14] Intra-arterial pressure was recorded before the first and after the last output determinations. No significant differences in blood pressure or in hematocrit value occurred between the first and last output measurements in a given individual.

RESULTS

Fick determinations were compared with intrathoracic dye injection in 54 studies in 36 patients (fig. 2). Good agreement between individual Fick and dye estimates was found. In 43 of the total 54 comparisons, cardiac index estimated by dye dilution was within 12.5 per cent of the Fick estimate, and in no case was the difference greater than 25 per cent. Average cardiac index determined by the Fick method was 2.44 L. per minute per M.^{2} and by the dye method the average value was 2.36 L. per minute per M.^{2} The averages of the two methods differed by 0.08 L. per minute per M.^{2} (3 per cent). Standard deviation of the individual differences between repeat determinations of cardiac out-

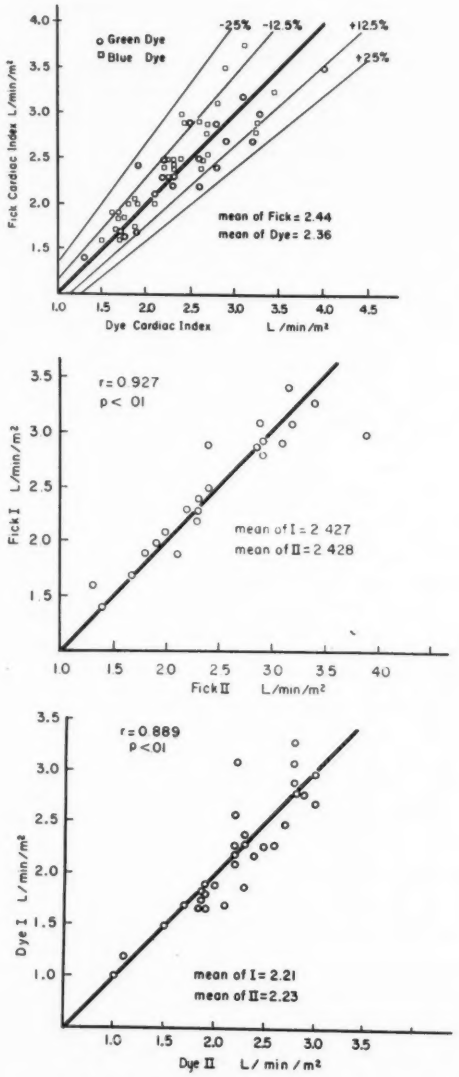


FIG. 2 *Top.* Comparison of cardiac index measured by indicator-dilution with nearly simultaneous estimates by the Fick method in the same subjects. *Heavy line* joins points indicating equal estimates by both methods. The difference between the means is 3 per cent (0.08 L. per minute per M.²) of the Fick mean, and the standard deviation of the individual differences between Fick and dye values is 0.29 L. per minute per M.²

FIG. 3 *Middle.* The reproducibility of the Fick measurement. *Points,* comparison of an estimate of cardiac index by the Fick method with another estimate by the same method a few minutes later under the same experimental conditions. Standard deviation of the differences between 2 successive determinations in the same subject is 0.27 L. per minute per M.²

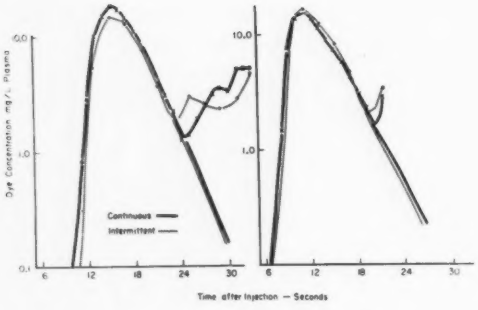
FIG. 4 *Bottom.* The reproducibility of dye estimates. *Points,* a comparison of an estimate of cardiac index by the dye-dilution method with another estimate a few minutes later under the same experimental conditions. Standard deviation of the difference between 2 successive determinations in the same subject is 0.26 L. per minute per M.²

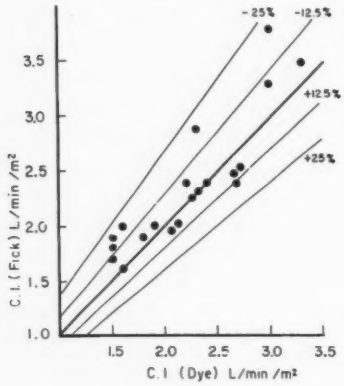
put in the same patient by the Fick method and by the dye method was 0.29 L. per minute per M.² The means were not significantly different as evaluated by the standard Fisher *t* test.

The variability between 2 Fick determinations in the same subject was about the same as that between 2 successive dye estimates. Figure 3 compares the cardiac index obtained by the first Fick estimate with that by the second Fick estimate in the same patient. Figure 4 shows similar comparisons of 2 dye estimates in the same subject.

The continuous densitometeric recording method used in these studies was compared with the classic intermittent sampling technic of Hamilton in 2 experiments. Dye was injected into the pulmonary artery. The densitometer continuously recorded dye concentration in brachial artery blood, while at the same time intermittent samples were collected from a femoral artery at 2-second intervals through a no.-17 needle and 3-inch length of Clay-Adams polyethylene 190 tubing. Plasma from each of the intermittent samples was diluted 1:9, and concentration of indocyanine-green dye was measured with a Beckman model B spectrophotometer. Figure 5 shows the curves of plasma dye concentration obtained by both technics and demonstrates close agreement observed in both trials.

Measurement of cardiac output by injection of dye into an antecubital vein was compared with estimates by the Fick method, in order to explore further the value of arm-vein dye injection in estimation of cardiac output. Dye was injected through a no. 15





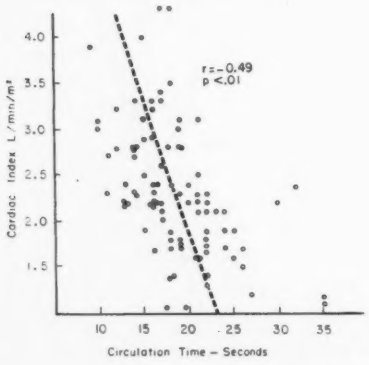


FIG. 5 *Top.* Dye-dilution curves obtained by continuous and intermittent sampling technics. Each pair of curves records simultaneous determinations by the 2 technics in a given subject.

FIG. 6 *Middle.* Comparison of cardiac index estimates from antecubital vein dye injection (*horizontal axis*) with estimates obtained by Fick method in the same subjects. Mean of the dye values was 2.3 L. per minute per M.^{2} Average of the Fick determinations was 2.3 L. per minute per M.^{2} Standard deviation of the differences between individual determinations was 0.28 L. per minute per M.^{2}

or 17 needle and was followed immediately by 20 ml. of saline solution to propel the bolus of dye promptly into the central circulation. Figure 6 demonstrates the comparison of antecubital dye injection and Fick estimates of cardiac index. In 14 of 20 determinations, cardiac index measured by forearm dye injection was within 12.5 per cent of the Fick index, and in no instance was the difference between the 2 so great as 25 per cent. In 11 of the 20 determinations the Fick estimate was higher than the dye value, but average values were not significantly different. (Fick, 2.42 L. per minute per M.^{2}; dye, 2.25 L. per minute per M.^{2})

Following arm-vein dye injection, circulation time (to peak of curve) averaged 28 seconds, with individual values ranging from 18 to 57 seconds. These values were distinctly more prolonged than circulation times obtained with intrathoracic dye injection, which averaged 18 seconds, individual determinations varying from 10 to 27 seconds. Although there was definite correlation between circulation time and cardiac output in the entire group, figure 7 demonstrates the wide variation in cardiac index associated with any given value of circulation time.

Indocyanine-green dye has been administered to 45 patients in these and related studies. Individual doses have ranged from 5 to 15 mg., and total doses in individual patients have reached 60 mg. The dye has produced no toxic effects, nor has skin discoloration been observed. Green color, detectable by the densitometer, disappeared from the plasma in 15 minutes. Observations of urine sediment, serum bilirubin, white blood count, and hematocrit level, made 20 hours following multiple injections of the dye in 10 individuals, showed no change from preinjection values.

FIG. 7 *Bottom.* Relation between circulation time and cardiac index. Circulation times are the times from intrathoracic dye injection to the peak of the dye curve. Cardiac indexes are those calculated from the same dye curve in which the circulation time was measured.

Discussion

The data demonstrate satisfactory agreement between dye and Fick estimates of cardiac output in patients with heart disease, and suggest that densitometric recording is sufficiently accurate for practical purposes. Table 1 presents data available in the English literature comparing Fick with dye estimates. In addition, Ring et al.,[15] have presented comparison of the Wood cuvette oximeter with the intermittent-sampling technic for measurement of cardiac output by dye dilution. They demonstrated good agreement, in 24 comparisons in 12 subjects, the difference between the 2 methods averaging 2 per cent. No individual difference exceeded 8 per cent.

These empiric demonstrations of close agreement between 2 quite different approaches to measurement of cardiac output buttress the solid theoretic bases of each method to lend support to the conclusion that both technics accurately estimate the volume of blood pumped by the heart. In individual subjects, slight differences between Fick and dye estimates are not surprising, since the dye method records average output during a 30-second period, while the Fick procedure calculates average cardiac output for a 5-minute period. Close agreement between successive Fick and dye determinations implies a remarkably steady state existing during the 30 minutes required to record 2 Fick and 2 dye measurements.

Advantages of Densitometric Measurement. The greatest single advantage of photocell recording of dye-dilution curves over the classic intermittent-sampling method of Hamilton lies in the ability of the investigator to visualize the curve as it is sampled rather than hours later. Unsatisfactory curves can be repeated at once. The sensitivity of the instrument has allowed routine recording of excellent curves following injection of only 10 mg. of Evans blue dye, permitting 4 successive determinations of cardiac output in the same subject without blue discoloration of the skin. Convenience in recording the dye curve and reduction of blood lost during sampling represent further advantages of densitometer recording. The small volume of the cuvette (0.04 ml.) allows complete replacement of the blood in the cuvette many times in each second, so that a very large number of individual values of dye concentration are available for plotting. This factor is of particular value in rapidly changing dye curves, for instance in the localization of right-to-left intracardiac shunts.

Disadvantages. The most serious disadvantages of this method centered around the calibration procedure used with Evans blue dye. About 100 ml. of blood were collected from each subject for calibration purposes. Addition of 0.2 ml., 0.4 ml., and 0.6 ml. of 5 per cent Evans blue to 20 ml. of blood gave optimal deflections in the recording system used. Accurate delivery of these small volumes of dye into the blood under anaerobic conditions represented a difficult problem. In an annoying minority of the determinations, perfectly good dye curves could not be used

Table 1.—*Comparisons, by Others, of Fick and Dye-Dilution Technics*

Authors	Number of comparisons	Average cardiac index (L./min./M.²) Fick	Dye	"% Error" Fick-dye ×100÷ Fick
Doyle[2]	78*	3.06	2.86	7
Neely[3]	39†	3.29	3.85	—17
Hamilton[4]	48‡	4.04	4.22	— 5
Werko[5]	69§	3.39	3.53	— 4
Kopelman and Lee[6]	28¶	2.54#	2.54	0
Nicholson[17]	8°	2.61	2.73	— 5
Friedlich[18]	9°	3.40	3.03	11
Present series	48	2.44	2.36	3

*Fifty-three normal, 25 with heart disease, functional classes I-IV.

†Twenty-two normal subjects.

‡Seven normal and 24 patients with heart and lung disease. Six determinations during exercise.

§Six normal; rest hypertensive, rheumatic heart disease, cor pulmonale, functional classes I-IV.

¶Ten normal, 10 rheumatic heart disease with mitral stenosis, 8 with left ventricular failure.

#Data given by authors for cardiac output only. Figures presented are authors' means divided by 1.73.

°"Patients with cardiovascular abnormalities." Dye curves recorded continuously.

for calculation of cardiac output because of obviously nonlinear calibration. A sufficient number of calibrations was recorded in which a straight line connected the origin and 3 dye concentrations to indicate that deflection of the recorder was linearly related to dye concentration in whole blood, and that nonlinear calibration was caused by errors in pipetting the dye. The disadvantages, inherent in this calibration procedure, led in the more recent measurements using green dye, to the use of the calibration method of Theilen et al.[11] in which blood collected during actual inscription of the dye curves is used for calibration, with reduction of blood shed and avoidance of pipetting errors.

Agreement between Fick estimates of cardiac output and those obtained by antecubital dye injection reemphasizes an additional advantage of the dye method; namely, its usefulness in patients in whom cardiac catheterization is inconvenient or inadvisable. Dye curves tend to be more spread out and to have lower peaks as the injection site is moved farther from the sampling site,[16] and occasionally curves obtained by arm-vein injection are so flat as to be useless, particularly in patients with marked valvular regurgitation or great increase in pulmonary blood volume. In such instances, a larger dose of dye may prove useful, but intrathoracic injection of dye is often necessary.

Indocyanine-green dye[10] has proved nontoxic, of good optical density, and easy to handle. Its chief advantage over Evans blue dye lies in the fact that it may be administered repeatedly without skin discoloration. Both its color and the rapidity with which it is cleared from plasma contribute to this useful feature. A second advantage of indocyanine-green dye relates to its wavelength of maximum light absorption, 800 mμ., a wavelength at which oxygenated and reduced hemoglobin absorb light equally. With the densitometer filters chosen to transmit to the photocell light of this wavelength, the output of the photocell is practically independent of the oxygen saturation of the blood. The desitometer, therefore, recognizes changes in hemoglobin saturation very poorly, and dye curves are uninfluenced by marked fluctuation in the oxygen content of the blood. Fading of color and aggregation of dye particles have not been a problem if green dye is dissolved first in the diluent supplied with the dye and then in plasma. Fading is rapid in water or saline solutions.

Summary

Continuous recording of dye concentration in blood by means of a photoelectric densitometer has proved a convenient technic for estimation of cardiac output by the indicator-dilution principle. Comparison of this technic with the Fick method has demonstrated close agreement in 48 human subjects with heart disease. Though most of the dye curves were produced by intracardiac dye injection, antecubital vein injection also produced estimates of cardiac output that compared favorably with nearly simultaneous Fick estimates.

The close agreement observed empirically between these widely different approaches to measurement of cardiac output supports the theoretic bases of the 2 methods in suggesting that cardiac output can be accurately estimated in the intact human, with ease and convenience.

Acknowledgment

The authors wish to thank Dr. W. T. Thompson, Jr., for criticism and advice, and Drs. D. S. Clark and Gordon Cavell for performing many of the cardiac catheterizations. The expert technical assistance of Mrs. Marjorie Stephenson, Mrs. Eunice Donald, and Misses Carol Alcock and Mary Andre is gratefully acknowledged. Indocyanine-green dye was supplied as "Cardiogreen" through the courtesy of Dr. John Brewer of Hynson, Westcott, and Dunning, Baltimore, Md.

Summario in Interlingua

Le registration continue del concentration de colorante in le sanguine per medio de un densitometro photoelectric se ha provate un convenibile technica in le estimation del rendimento cardiac super le base del principio del dilution de indicatores. Le comparation de iste technica con le methodo de Fick in 48

subjectos human con morbo cardiac ha demonstrate un alte grado de concordantia. Le majoritate del curvas de colorante esseva basate super injectiones intracardiac, sed injectiones in venas antecubital resultava etiam in estimationes de rendimento cardiac ben comparabile con illos de quasi simultanee estimationes secundo le methodo de Fick.

Le intime concordantia empiricamente observate inter iste differentissime methodos pro le measuration del rendimento cardiac supporta le bases theoric de ille methodos. Le ultime conclusion practic pare esser que le rendimento cardiac pote esser determinate accuratemente in humanos intacte e que le procedimentos technic que es requirite in tal determinationes es facile e convenibile.

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Atherosclerosis in the Bantu

By JACK P. STRONG, M.D., JOHN WAINWRIGHT, M.D., AND HENRY C. MCGILL, JR., M.D.

The aortic lesions of atherosclerosis in Bantu, aged 1 to 40 years, have been studied in 241 autopsied cases from Durban, South Africa. The findings are compared with those from a similar study of white and Negro cases in New Orleans, La. The relationship of incidence and quantitative extent of aortic fatty streaks and fibrous plaques to race, environment, blood lipid levels, coagulation factors, and clinical manifestations of atherosclerosis is discussed.

THE Bantu population in South Africa is of great medical interest because of the growing body of evidence that this group is less subject to the fatal sequelae of atherosclerosis than North Americans and Europeans.

An analysis of cardiovascular disease in 3,000 consecutive autopsies on Bantu and Coloured at Johannesburg General Hospital by Becker in 1946 revealed atheroma as a direct cause of death in only 0.4 per cent of the cases.[1] Higginson and Pepler in 1954 mentioned the widespread clinical belief that the more severe complications of atherosclerosis such as cerebral and coronary thrombosis are rare among the Bantu, and in their analysis of records from 1,328 consecutive autopsies found only 7 cases of coronary thrombosis and myocardial infarction.[2] Vogelpoel and Schrire in 1955 studied the incidence of myocardial infarction in Capetown as shown by electrocardiography and found that it was rare in the Bantu, more common in the Cape Coloured and still more frequent in the European.[3] In another electrocardiographic survey in 1958 Schrire reported essentially similar findings.[4] Analysis of autopsy material in Durban, South Africa (table 1) indicates that myocardial infarcts in Bantu are much less common than in Europeans from Durban in the same age groups. Even in older individuals, cases of myocardial infarction are extremely rare in the Bantu.

Thus, the cumulative evidence from a wide variety of sources is quite convincing that myocardial infarction is rare in the Bantu. There has been a tendency, however, to interpret this observation as an indication that the Bantu is free of atherosclerosis or only rarely involved by atherosclerosis.

It is important to distinguish clearly between the incidence and extent of the arterial lesions of atherosclerosis and the incidence of clinically manifest disease due to atherosclerosis. Although, as previously stated, Becker reported that atheroma was the direct cause of death in only a small percentage of autopsy cases studied, he found that atheroma was the most common of all the cardiovascular lesions present, occurring in 27.5 per cent of routine postmortem examinations.[1] In comparing his data with results of autopsy studies appearing in the literature, he concluded that the incidence of atherosclerosis in the Bantu up to the age of 45 years is not far removed from that in other races; its incidence in the succeeding years, especially in advanced age, may be slightly less. In their comparative study Higginson and Pepler came to the conclusion that severe atherosclerosis is relatively infrequent among the Bantu in comparison with Danish cases; that there is less coronary sclerosis and occlusion than in the United States; and that aortic atherosclerosis is less severe in the Bantu than in Europeans living in

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South Africa.[2] Laurie and Woods disagreed with the view that atherosclerosis is rare in the Bantu.[5] On the basis of autopsy studies they have reported that aortic atherosclerosis is common.

If myocardial infarction is much less common in the Bantu than in other populations, it is highly desirable to know the relative incidence and extent of the arterial lesions of atherosclerosis. Such data will yield valuable information concerning the pathogenesis of atherosclerotic lesions and their relationship to clinically manifest disease.

This report is a comparison of the early aortic lesions in autopsy material from South Africa and the United States collected and preserved in an identical manner and examined by the same observers. Three distinct groups considered in this report are the South African Bantu, the New Orleans Negro, and the New Orleans white man. The present study has been restricted to individuals of ages 1 to 40 years for reasons cited in previous reports on the New Orleans material.[6, 7]

Materials and Methods

Aortas were collected from 241 necropsies of Bantu between 1 and 40 years of age at King Edward VIII Hospital, Durban, South Africa, and from 461 necropsies of white and Negro subjects at Charity Hospital of Louisiana at New Orleans and the office of the Coroner, Parish of Orleans (table 2). Data on the New Orleans cases have been presented in some detail in a previous report.[6] The specimens from South Africa and New Orleans were processed in an identical manner. After dissection and fixation in 10 per cent formalin, the specimens were stained with Sudan IV and packaged in transparent plastic bags.[8] Evaluation of lesions from both geographic areas for this study were made by the same observers (J.P.S. and H.C.M.). Regrading of the Bantu material by J.W. was in close agreement with the initial grading. The grading system was based on estimated percentage of intimal surface of the aorta involved by fatty streaks, fibrous plaques, and complicated lesions. Definitions and illustrations of these different types of lesions have been given in detail previously.[6] Figure 1 demonstrates fatty streaks in 2 aortas of Bantu after staining with Sudan IV. Fatty streaks are flat or slightly elevated pale yellow patches, flecks, and streaks which are stained selectively by fat stains. Fibrous plaques are elevated gray white glistening intimal plaques. Complicated lesions are those plaques with ulceration, calcification, thrombosis, or hemorrhage.

Table 1.—*Myocardial Infarcts in Series of Consecutive Autopsied Cases, 1951-1958, in Durban, South Africa*

Age in years	Sex	Bantu			Europeans		
		Total cases autopsied	Cases of myocardial infarction	Per cent autopsies with myocardial infarction	Total cases autopsied	Cases of myocardial infarction	Per cent autopsies with myocardial infarction
21-40	M	566	3	.5	64	5	7.8
	F	482	0	0	48	2	4.2
41-60	M	616	6	1	290	33	11.4
	F	301	0	0	163	12	7.3
61 and over	M	201	1	.5	468	62	11.1
	F	120	0	0	301	39	13.0

Table 2.—*Seven Hundred and Two Aortas from Cases Age 1 to 40 years*

	Male	Female	Total
Bantu	123	118	241
New Orleans Negro	162	137	299
New Orleans white	102	60	162
Total	387	315	702

Results

The results are presented in tables 3 and 4. Complicated lesions as defined above were insignificant in all groups. The average extent of each type of lesion in the Bantu is depicted graphically in figures 2 and 4. The average extent of involvement in Bantu and New Orleans cases is compared in figures 3 and 5.

Fatty Streaks

Aortic fatty streaks are present in many of the Bantu cases in the first decade as seen in table 3. After the first decade all of the Bantu cases have fatty streaks to some degree. The prevalence of fatty streaks in the Bantu is similar to that in the New Orleans Negro and white cases.

TABLE 3.—*Distribution of Aortas by Age and Per Cent Surface Covered by Fatty Streaks*

Per cent surface involved	Bantu age								New Orleans Negro age								New Orleans white age							
	1-5	6-10	11-15	16-20	21-25	26-30	31-35	36-40	1-5	6-10	11-15	16-20	21-25	26-30	31-35	36-40	1-5	6-10	11-15	16-20	21-25	26-30	31-35	36-40
Male																								
0	4					1			9								5							
<1	2	3						1	24	1						1	9	2						
1-5	4	4	4			3		1	17	8	1	1	3	1		6	4	8	3		2	2		1
6-10			1	3	2	6	3	2	2	5		5	5	3	3	6		2	3	3	6	2	2	
11-20		1	2	3	1	6	8	10	2	1	4	5	3	5	1	2			2	5	4	5	2	9
21-30			3	6	3	7	4	11			4	6	2	2	6	2				1	4	2	1	2
31-50				2	4	1		7			4	3		1	2	1				1	3		2	1
51-75								1					1	1	2					1		1	1	1
76-100											1													
Total cases	10	8	10	14	10	24	15	32	54	15	14	20	14	13	14	18	18	12	8	11	19	12	8	14
Average per cent surface involvement	1	4	12	21	27	15	16	26	2	5	29	19	15	20	28	18	1	3	8	21	18	17	27	21
Female																								
0	4	1							2								2							
<1	2								24	1							8	1			1			
1-5	3	1	1		1	4	1		14	9			1	1	1		1	1	2	3		2	1	
6-10				1		3	2	5	2		1			1	2	1			3		1	2	2	4
11-20	1		2	6	4	6	7	7	1	1	1	3	6	8	2	2		1		3	2	2	3	5
21-30			1	2	5	15	5	7			6	3	3	8	6	11						2		4
31-50				1	4	3	5	2				2	1	3	1	3					1	1	1	
51-75					2		2	1			1		1	1	3								1	
76-100							1																	
Total cases	10	2	4	10	16	31	23	22	43	11	9	8	12	22	15	17	11	3	5	6	5	9	8	13
Average per cent surface involvement	2	2	14	19	30	20	29	21	2	4	26	25	22	23	28	26	1	6	6	9	16	16	21	16

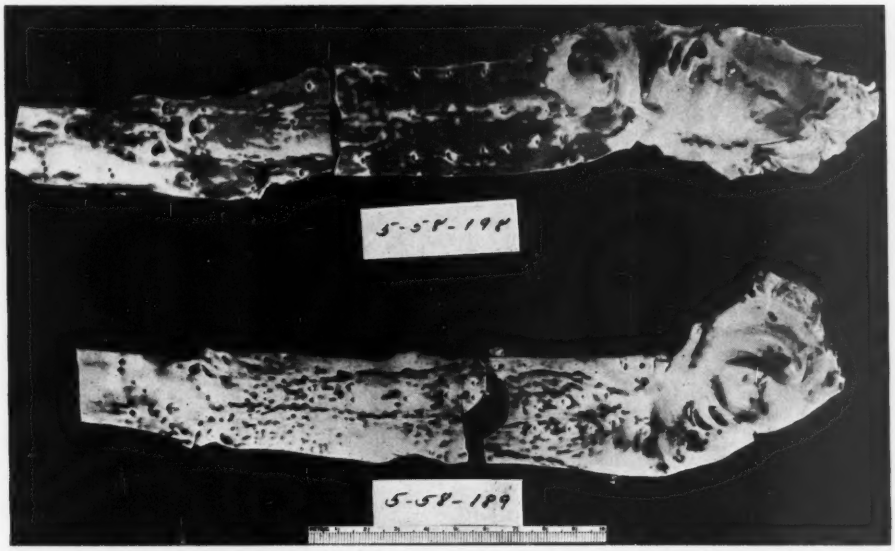

FIG. 1. Aortas from Bantu demonstrating fatty streaks. The aortas have been stained grossly with Sudan IV. Fatty streaks appear black in this photograph. Aorta 5-58-198 from a 19-year-old Bantu man, who died from pulmonary tuberculosis, was graded as 45 per cent surface involvement with fatty streaks. Aorta 5-58-189 from a 15-year Bantu girl, who died from pulmonary tuberculosis, was graded as 18 per cent surface involvement with fatty streaks. There are no fibrous plaques or complicated lesions in either specimen.

The average percentages of the intimal surface of the aorta involved with fatty streaks in male and female Bantu are shown in figure 2. There is only a small amount of surface involvement in the first decade followed by a sharp increase in both sexes in the second decade. This rapid rise reaches a peak in the 21 to 25 year age group. After this period there is a leveling off and apparent regression of fatty streaking until the fourth decade. There is no consistent sex difference in fatty streaks although from 21 to 36 years of age, women show slightly more average surface involvement than men.

It should be emphasized that while averages are being compared in figure 2 and subsequently in figures 3 to 5, there is considerable variation in the quantitative degree of surface involvement in each age, sex, and race group (tables 3 and 4).

Sex-adjusted averages for surface involvement with fatty streaks in Bantu, New Orleans Negro, and New Orleans white cases are compared in figure 3. In the 11 to 15 year age group in which there is a striking difference between New Orleans Negro and New Orleans white, the Bantu have an intermediate degree of fatty streaks. The possible significance of the differences between Negro and white adolescents in New Orleans has been discussed in the original report.[6] In the other age groups there are no consistent differences between Bantu and New Orleans cases.

Fibrous Plaques

In contrast to the similarity in prevalence of fatty streaks, fibrous plaques are much less prevalent in the Bantu than in either New Orleans group. For example, 40 per cent of the Bantu in the fourth decade have fibrous plaques while 90 per cent of both Negro and white cases in New Orleans have fibrous plaques. Quantitatively, in terms of average per cent surface involvement, the difference is even greater.

Surface involvement with fibrous plaques

TABLE 4.—*Distribution of Aortas by Age and Per Cent Surface Covered by Fibrous Plaques*

Per cent surface involved	Bantu age								New Orleans Negro age								New Orleans white age							
	1-5	6-10	11-15	16-20	21-25	26-30	31-35	36-40	1-5	6-10	11-15	16-20	21-25	26-30	31-35	36-40	1-5	6-10	11-15	16-20	21-25	26-30	31-35	36-40
Male																								
0	10	8	9	14	8	17	10	12	54	15	12	14	12	6	2	2	18	12	8	10	13	8		1
<1					1		1	2				4	1	2		2					3	1	1	1
1-5			1		1	5	2	13			2	2	1	4	6	7				1	3	2	4	1
6-10						1	1	2							2	2								6
11-20								3						1	3	5						1	1	3
21-30						1	1																2	1
31-50																								
51-75															1									
76-100																								
Total cases	10	8	10	14	10	24	15	32	54	15	14	20	14	13	14	18	18	12	8	11	19	12	8	14
Average per cent surface involvement	0	0	<1	0	<1	2	3	3	0	0	<1	<1	<1	2	10	6	0	0	0	<1	<1	2	10	12
Female																								
0	10	2	4	9	15	27	17	14	43	11	9	8	11	10	3	1	11	3	5	6	4	6	1	1
<1						1	3	1					1	5	3	1					1		2	1
1-5					1	3	1	4						3	7	6						2	3	3
6-10							1	2						1	2	4								1
11-20							1	1								2						1	1	3
21-30				1												1								1
31-50														1		2								2
51-75														2									1	1
76-100																								
Total cases	10	2	4	10	16	31	23	22	43	11	9	8	12	22	15	17	11	3	5	6	5	9	8	13
Average per cent surface involvement	0	0	0	2	<1	<1	1	2	0	0	0	0	<1	8	3	11	0	0	0	0	<1	2	11	18

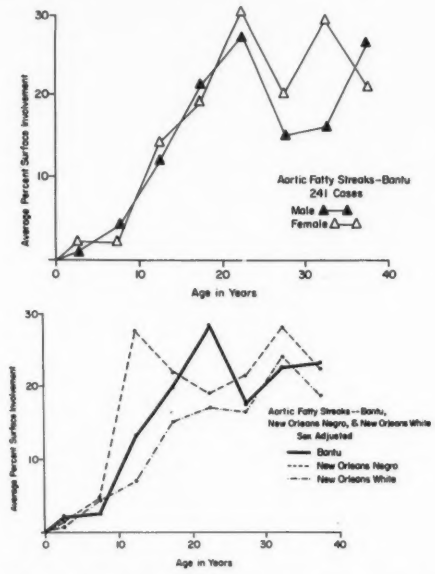

FIG. 2 *Top.* Aortic fatty streaks—Bantu, 241 cases.

FIG. 3 *Bottom.* Aortic fatty streaks—Bantu, New Orleans Negro, and New Orleans white, sex-adjusted.

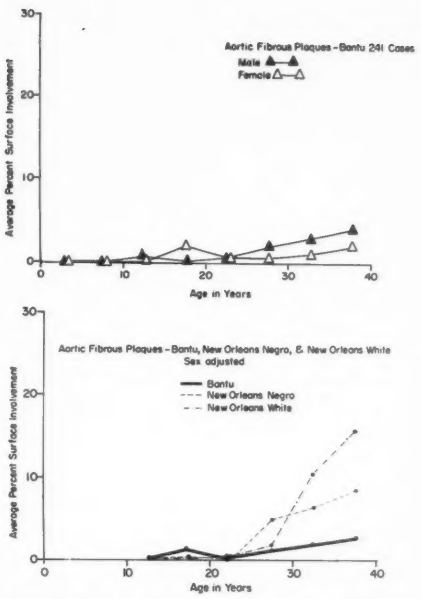

FIG. 4 *Top.* Aortic fibrous plaques—Bantu, 241 cases.

FIG. 5 *Bottom.* Aortic fibrous plaques—Bantu, New Orleans Negro, and New Orleans white, sex-adjusted.

is quite low in the Bantu. In figure 4 the average per cent of intimal surface involved by fibrous plaques in male and female Bantu is compared. In the fourth decade the males have slightly more surface involvement than females. In figure 5 the sex-adjusted average in Bantu is compared with the New Orleans cases. The Bantu have much less of the intimal surface of the aorta covered by fibrous plaques than either New Orleans group. In the 36 to 40 year age group the average value for Bantu is 3 per cent as compared to 8 per cent in the New Orleans Negro and 15 per cent in the New Orleans white group. These differences are significant by t test. (Bantu man vs. New Orleans white man, 36 to 40 years. $p < .001$; Bantu woman vs. New Orleans white woman 36-40 years $p < .001$; Bantu man vs. New Orleans Negro 36-40 years $p < .05$; Bantu woman vs. New Orleans Negro woman, 36-40 years $p < .01$.)

Complicated Lesions

Lesions with calcification, hemorrhage, thrombosis, or ulceration were uncommon in all groups, and when present, usually consisted of small areas of calcification. Quantitatively, average surface involvement with complicated lesions was insignificant in each of the 3 population groups.

Total Intimal Surface Involved

Total surface covered by all types of lesions is for practical purposes the sum of fatty streaks and fibrous plaques. In the fourth decade total surface involvement was greater in the New Orleans white group and least in the Bantu.

Relationship of Findings to Living Population

Relating the findings from a study of autopsy material to the respective living populations is a desirable but difficult goal. Possible biases in selection can only be mentioned and attempts were made to control as many as possible. One such source of possible bias is the presence within the 3 groups of unequal numbers of cases of hypertension, diabetes

TABLE 5.—*Average Per Cent of Aortic Intimal Surface Involved with Fibrous Plaques after Exclusion of Cases with Hypertension, Diabetes Mellitus, and Death due to Atherosclerosis*

	Bantu		New Orleans Negro		New Orleans white	
Sex	M	F	M	F	M	F
Age in years						
1-10	0	0	0	0	0	0
11-20	<1	0	<1	0	<1	0
21-30	2	<1	1	3	1	<1
31-40	3	1	5	2	10	6

TABLE 6.—*Comparison of Per Cent Average Surface Involvement of Aorta in Accidental Deaths, Bantu and New Orleans Men*

	21-30 years			31-40 years		
	Bantu	New Orleans Negro	New Orleans white	Bantu	New Orleans Negro	New Orleans white
No. of cases	10	16	17	8	14	7
Average surface involvement with						
Fatty streaks	16	16	20	21	18	29
Fibrous plaques	<1	<1	<1	<1	3	12

mellitus, myocardial infarction, encephalomalacia, and other clinically evident sequelae of atherosclerosis, that is, conditions which are generally believed to be associated with greater than average atherosclerosis. For example, there were 7 deaths due to coronary atherosclerosis in the New Orleans white group and none in the other 2 groups. To eliminate this possible bias the average extent of fibrous plaques was calculated for each group after the removal of 77 cases falling in the categories mentioned above, leaving a total of 625 cases from the original 702. As seen in table 5, the average per cent of surface involvement with fibrous plaques is lowered for each group, but the previously described differences between the 3 groups remain unchanged. This outcome indicates that there is a substantial difference in extent of aortic fibrous plaques among the 3 populations, even among individuals who die from conditions not due to atherosclerosis and who do not have hypertension or diabetes. Analysis of fatty streaks in the 625 cases showed no changes from previous results.

Another means of testing the applicability of these data to the living population is shown in table 6, where only accidental or traumatic deaths are considered. There was a sufficient number of cases of this type only in men 21 to 40 years of age. The results yield substantially the same relationships for both fatty streaks and fibrous plaques as described above.

DISCUSSION

In this comparison of aortic lesions in autopsied cases of South African Bantu, New Orleans Negro and New Orleans white man it has been clearly shown that the prevalence and quantitative extent of fatty streaking is quite similar in all groups despite great differences in environmental and racial background. Despite the similarity in fatty streaking, fibrous plaques develop to a lesser extent in the Bantu and appear to parallel certain other suspected or reported differences between Bantu and other populations.

The characteristics of the Bantu population have been summarized in an excellent review by Walker.[9] Dietary fat intake and serum cholesterol levels are reported to be lower in the Bantu than in North Americans and in Europeans living in South Africa.[10-13] The results of this study would indicate that there is no correlation between the amount of fatty streaks and these factors before age 40. However, it appears that the extent of aortic fibrous plaques is correlated with all these factors, although the mechanism of the association is not known. It should be kept in mind in this respect that there are many differences between the Bantu and the other 2 populations aside from the ones previously mentioned, such as dietary protein, estrogen levels, liver disease, plasma-protein patterns, amount of physical activity, and numerous socioeconomic factors.[9]

Whether the differences in fibrous plaques

among the 3 groups are due primarily to environmental or racial and genetic factors cannot be determined with certainty from this study. The Bantu and New Orleans Negro are not strictly identical racially, but a difference between the groups of negroid people suggests that environmental factors may be at least partially responsible for the difference. The fact that there is a greater difference in fibrous plaques between Bantu and New Orleans white man than Bantu and New Orleans Negro suggests that a difference in genetically determined "susceptibility" may also exist. Studying other Negro and white populations under a variety of environmental conditions should help resolve the problem of the relative importance of these factors.

The fact that aortic fibrous plaques in the fourth decade tend to parallel population differences in myocardial infarction indicates that lesions of aortic atherosclerosis very likely reflect the degree of coronary atherosclerosis, at least on a group basis. Nevertheless, a similar comparative study of the coronary arteries is imperative and has been initiated.

The dichotomy in the pattern of fatty-streak and fibrous-plaque development deserves comment, especially since fatty streaks precede fibrous plaques and are generally believed to be the first stage of atherosclerosis. One possible explanation for a greater amount of fibrous plaques developing in a group with the same quantitative degree of fatty streaks as another may be that the lipid present in fatty streaks in different areas is qualitatively different. Chemical analyses on gross specimens of aortas from Bantu and Europeans[14] have shown that in aortas graded equally the mean chemical composition was similar for both races in specimens with mild to moderate atherosclerosis. In severe atherosclerosis with similar surface involvement the percentage composition in the races differed considerably with dry weight, ash and calcium, cholesterol being more marked in the white series. These studies still do not answer the questions raised by the present study concerning the precise lipid composition of the fatty streak. More refined methods of microchemical determination of lipids, such as vapor-phase chromatography, may make possible an answer to these questions.

There also is a possibility that progression of fatty streaks to fibrous plaques may be related to the process of fibrin deposition, thrombosis, and organization or to vascularization and hemorrhage within fatty streaks. Several studies on blood coagulation factors in the Bantu have been reported. Gillman, Naidoo, and Hathorn[15] found high levels of fibrinolysins in the Bantu. Merskey, Gordon, and Lackner[11] noted that fibrinolysis was more rapid in the Bantu than in the white. However, they could not demonstrate any other differences in blood coagulation that would indicate that the Bantu is less liable to thrombosis than Europeans. It is conceivable that a decreased tendency to thrombosis in the Bantu might be responsible for both a decreased amount of atherosclerotic lesions (fibrous plaques) and lower incidence of myocardial infarction. We have found no evidence in our studies of the natural history of atherosclerosis to indicate that mural thrombi precede the formation of fatty streaks. However, it is possible that fatty streaks, as sites of tissue damage, are subject to fibrin encrustation and thereby are converted to fibrous plaque. This hypothesis is attractive in view of the experimental studies of O'Neal and Thomas, which indicate that there is an affinity between fat and fibrin.[16] At the present time, however, there is little evidence for this in the human.

Regardless of the relationship of fatty streaks to fibrous plaques, the latter appear to be a key factor in the pathogenesis of atherosclerosis for they are the earliest of the arterial lesions of atherosclerosis to be positively correlated with the clinically manifest sequelae of atherosclerosis.

Summary

The natural history of aortic atherosclerosis in the Bantu, of Durban, South Africa, age 1 to 40 years, is compared to that of the

New Orleans Negro and white man in the same age group. Fatty streaks are present universally in all 3 groups to some extent after the first decade. The average surface involvement with fatty streaks is not appreciably different in the 3 groups .The prevalence and quantitative extent of fibrous plaques are much less in the Bantu than in the New Orleans Negro and New Orleans white man. This difference does not appear to be due to sampling bias by selection of autopsies. The degree of aortic fatty streaking in early life is not correlated with reported group differences in dietary fat intake, serum cholesterol levels, and the incidence of clinical manifestations of atherosclerosis in later life. The degree of aortic fibrous plaques in the fourth decade does parallel the reported racial and geographic differences in these factors.

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Summario in Interlingua

Le historia natural de atherosclerosis aortic in bantus de Durban in Sud-Africa de etates de inter 1 e 40 annos es comparate con illo in respresentantes del racias negre e blanc de Nove Orleans in le mesme gruppo de etate. Strias grasse es presente universalmente in le 3 categorias a varie grados post le prime decennio. Al media le affection de superficie con strias grasse non differe appreciabilemente inter le 3 categorias. Le prevalentia e le extension quantitative de placas fibrose es multo minus marcate in bantus que in negros e blancos de Nove Orleans. Iste differentia non pare esser le effecto de accidentes de selection del specimens necroptic. Le grado de striation grasse durante le prime phases del vita exhibi nulle correlation con le reportate differentia inter le 3 categorias con respecto al ingestion dietari de grassia, con respecto al nivellos seral de cholesterol, e con respecto al incidentia de manifestationes clinic de atherosclerosis a periodos plus avan tiate del vita. Le grado del placas fibrose i le aorta durante le quarte decennio del vita del altere latere, exhibi un parallela con l reportate differentias racial e geographi con respecto al factores mentionate.

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Goldberg, H., Dickens, J., Raber, G., and Hayes, E., Jr.: Simultaneous (Combined) Catheterization of the Left and Right Heart. Am. Heart J. **53**: 579 (April), 1957.

The data obtained from 33 simultaneous catheterizations of the left and right heart performed in 26 individuals (3 with normal cardiovascular systems, 12 with mitral stenosis, and 11 with aortic stenosis) are presented. In each patient, cardiac output and pressure gradients were obtained simultaneously and the orifice size was calculated. In mitral stenosis, a ventricular filling pressure gradient was found as a constant physiologic abnormality. Evaluation of the degree of stenosis, however, required a knowledge of the pressure-flow relationships as well as the gradient, since the latter was found to be influenced by the rate of blood flow across the mitral valve. The pressures within the pulmonary circuit were not necessarily a measure of the degree of stenosis. When the degree of mitral obstruction and the pulmonary vascular resistance were constant, the rate of blood flow varied with the height of the pulmonary artery pressure. When the degree of mitral obstruction and the rate of blood flow across the valve were constant, the degree of pulmonary vascular resistance was reflected by the height of the pulmonary artery pressure. In aortic stenosis, a pressure gradient across the aortic valve during ventricular systole was constantly found. In general the systemic blood flow was reduced and was a function of the pressure gradient and the degree of aortic obstruction. The gradient alone was not an accurate measure of the degree of obstruction. As a result of the ventricular hypertrophy in aortic stenosis the pressure-volume elasticity relationship of the left ventricle was altered, but this did not correlate with clinical left ventricular failure. The applicability of combined heart catheterization in evaluating patients for cardiac surgery and surgical technics for correction of stenotic lesions is demonstrated.

SAGALL

An Aortic-Right Ventricular Fistula of More than Eighteen Months' Duration

An Approach to Dynamics

By THEODORE T. BRONK, M.D., WILLIAM J. MCDERMID, M.D., AND SIMON RODBARD, M.D., PH.D.

A 79-year-old man who developed evidence suggesting an intracardiac shunt survived at least 18 months after its onset. Intracardiac mechanisms that may protect the pulmonary circulation from excessive flows are suggested, based on anatomic findings at necropsy.

THE establishment of a fistulous tract between the aorta and the right ventricle poses critical problems in cardiopulmonary dynamics. The higher aortic pressure drives an excessive flow of blood into the right ventricle and overloads it. The increased pulmonary arterial pressure and blood flow lead to pulmonary edema and right heart failure, thereby precipitating a fulminating course and early death in most patients who develop such a fistula.[1-13]

We have observed a patient with such a fistula that had been present for at least 18 months. Anatomic findings in the heart suggest a possible mechanism for the prolonged survival.

CASE REPORT

A 79-year-old white man was first admitted to Mount St. Mary's Hospital on November 21, 1954, complaining of severe shortness of breath. The patient had noted the onset of dyspnea about 4 years previously. Treatment with digitalis and Mercuhydrin gave definite improvement until 2 weeks prior to admission, when mental confusion, weakness, dyspnea, orthopnea, and ankle edema all became marked.

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The patient did heavy manual labor all his life and drank heavily for many years. From age 70, he worked as a gardener (mowing lawns and doing other moderately hard work) without difficulty until 4 years before death. Three years before death, a heart murmur was noted.

Examination in May 1954 revealed minimal exertional dyspnea with neither orthopnea nor dependent edema. On hospitalization in November 1954 he was in acute distress. A rough thrill was palpable over the precordium and a machinery murmur was heard over the entire chest, loudest along the left sternal border. The maximal impulse was at the left anterior axillary line. Breath sounds were indistinct, but numerous rales and rhonchi were heard bilaterally. The blood pressure was 162/40. A double femoral arterial sound (Duroziez) was present. The electrocardiogram showed delay in atrioventricular conduction, right bundle-branch block, and digitalis effect with runs of bigeminy. The white cell count was 27,000 per mm.^{3} initially but fell later to 16,000. Four blood cultures were negative. X-ray and fluoroscopy revealed marked cardiac enlargement. The clinical picture was considered compatible with ventricular septal defect, superimposed on arteriosclerotic heart disease. The patient improved markedly on digitalis and Mercuhydrin, and was discharged home.

The patient was readmitted 1 year later complaining of intermittent severe chest pain of 3 weeks' duration, not necessarily related to exertion. His general physical condition was unchanged, except for some progression of the congestive heart failure. Blood pressure was 246/60. The hemogram showed a hematocrit of 35, hemoglobin of 74 per cent, and white blood cell count of 16,000 per mm.^{3} Chest films showed an increase in the heart size and a progression of hilar

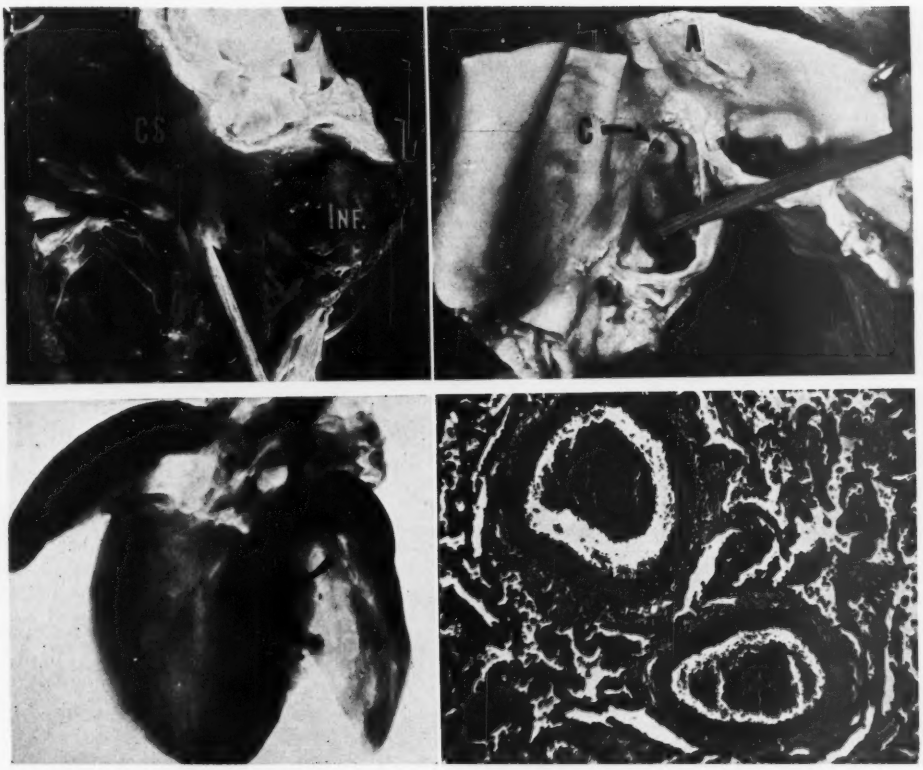

FIG. 1 *Top left.* The septal surface of the right ventricle is shown. A wooden probe is inserted into the fibrous orifice of the anomalous fistula. Immediately above the orifice, the hypertrophied crista supraventricularis (*CS*) is evident as a broad band extending from the left upper corner of the photograph to the right margin of the exposed muscle. The dilated infundibulum (*Inf.*) is seen above the crista on both the right and left sides of the opened ventricle. The pulmonary artery and valve are above.

FIG. 2 *Top right.* The probe extends from the fistula in the right coronary sinus, immediately below the right coronary artery (*C*). Aorta (*A*) is above.

FIG. 3 *Bottom left.* Radiograph of the heart showing the fistula at arrow, filled with radiopaque medium. The free walls of the right and left ventricles are on the right and left of the septum respectively.

FIG. 4 *Bottom right.* Masson trichrome stain of a section of lung showing severe vascular congestion with normal pulmonary vessels (× 100).

congestion with a suggestion of an inflammatory process in the right lung. The electrocardiogram continued to show delay in atrioventricular conduction, right bundle-branch block, and bigeminy.

Again the patient improved markedly with digitalis and Mercuhydrin. He was discharged to a nursing home after 10 days. Except for gradually increasing anasarca, his condition remained essentially unchanged until death on April 11, 1956.

The principal pathologic findings were in the heart, which was markedly enlarged, weighing 625 Gm. The right ventricular wall at the conus arteriosus was 7 mm. thick, and the left ventricular wall was 20 mm. thick. The conus, evident as a saccular dilatation immediately below the pulmonary valve, was clearly differentiated from the sinus of the right ventricle by a markedly hypertrophied supraventricular crest on the septal wall. Immediately below the crest a completely fibrotic band less than 1 cm. in circumference was seen at what appeared to be the junction of 2 columnae carneae (fig. 1). This opening led through a tract to an ovoid opening with rolled fibrotic edges 1 cm. in circumference, near the lower attachment

of the right coronary cusp (fig. 2). Marked calcification with some granular projections extended into the sinus of Valsalva at the attachment of the aortic cusp. The tract was funnel-shaped with its greatest circumference at the sinus of Valsalva. When it was filled with radiopaque material and x-rayed (fig. 3), a narrow diverticulum was demonstrated in the midportion of the tract extending somewhat beneath the muscle of the crista supraventricularis and ending blindly. The right coronary orifice was immediately above the opening of the tract but had no connection with it.

Microscopically, the fistulous tract was lined by flattened endothelial cells and encircled by a thick band of fibrosis, which in places was relatively hyalinized. In other regions, numerous elongated spindle cells with narrow elongated nuclei were present in parallel arrangement. Many elastic fibers were mixed with the fibrous tissue covering the tract. The right coronary artery and the circumflex branch of the left were patent, but showed considerable atheromatosis. The anterior descending branch of the left coronary artery was occluded by an old sclerotic, fibrotic process 3 cm. from its origin. The myocardium showed no gross evidence of recent or old infarction.

Regions of atelectasis with small foci of bronchopneumonia and bronchitis were present in both lower lobes. The pulmonary blood vessels, microscopically, were congested but showed no significant sclerosis (fig. 4).

Severe arterial and arteriolar nephrosclerosis was evident on microscopic section. Most of the small arteries and arterioles of the adrenal glands showed thickened walls with intimal fibrosis.

Discussion

The present case has interest from several points of view, including the mechanism of development of fistulas between the aorta and the chambers of the heart, the special dynamics induced by the abnormal blood flow in such instances, and the potential mechanism for protection against excessive pulmonary arterial pressures and flows.

Aneurysmal dilatations at the root of the aorta are known to extend in any direction and may produce a fistulous connection with any of the chambers of the heart, the pulmonary artery, and even with the pericardium.[14] These abnormal communications have been attributed to specific developmental defects of the heart and great vessels, especially when the fistulae are found in the young.[2, 10] In older individuals, these lesions are variously considered to result from congenital defects in the ventricular septum or from arteriosclerotic or other degenerative processes.[11, 13] Since these aneurysms and fistulas may point in almost any direction, the development of a particular type of fistula may be ascribed to the combination of the mechanical forces and any local site of weakness, rather than to a congenital anomaly.[4, 15] The present case history provides no evidence for a congenital defect. The presence of such a large fistula in the heart of a 79-year-old man whose history was that of a hard laborer strongly suggests that the lesion was acquired.

Erosion of the base of the aorta may lead to a burrowing through the ventricular septum, with the establishment of a new channel lined by endocardium. In the present instance, the extensive and specific pattern of development of endothelium, collagen, and elastic tissue suggests the action of mechanical forces in transforming the interventricular tissues into structures resembling a blood vessel under considerable mechanical tension.

Most cases with an acquired fistula report a signal event characterized by sudden pain in the chest or the upper abdomen and the immediate appearance of a loud continuous murmur near the sternum.[4] The development of the fistula may be more gradual, since no report of an acute episode could be elicited in our patient and in other reported cases.[15] Usually the development of a ventricular septal defect or an aortic-ventricular fistula leads to rapidly progressive congestive failure, sometimes associated with endocarditis. In the present instance, the fistula apparently was present for at least 18 months, and perhaps for the entire 6 years that the patient was under treatment for heart failure.

The murmurs and arterial pressures suggest that flow took place from the aorta into the right ventricle during most of the cycle. The machinery-like character of the murmur suggests that particularly during early ventricular systole, some of the flow may have

been pumped by the right ventricle into the aorta. Cardiac nodules at the aortic and ventricular orifices of the fistulous tract provide evidence for the reaction of these tissues to a strong stream.

The compatibility of such a large fistula with long survival is of considerable interest. In the presence of the fistula, the high aortic pressure would tend to drive a rapid flow of blood into the right ventricle, with a resulting excessive pulmonary blood flow. This increased flow may account for some of the pulmonary congestion, dyspnea, and signs of right heart failure.

Of particular interest in the present case was the site of the opening of the fistula immediately below the remarkably well developed supraventricular crest of the right ventricle. This muscle band, interposed between the ventricular opening of the fistula and the outflow tract of the chamber, has been implicated on the basis of phylogenetic[16] and cardiodynamic[17, 18] evidence as a mechanism protecting the pulmonary vasculature against excessive blood pressures and flows. In congenital ventricular septal defects, the high left ventricular pressures are transmitted directly to the right ventricle and then to the pulmonary vessels. Clinical evidence has suggested that in such cases, the supraventricular crest may act as a sphincter during midsystole to prevent these high pressures from being transmitted to the pulmonary vessels. The fact that the fistula entered the right ventricle below the markedly hypertrophied supraventricular crest would place the crest in a position to provide a degree of regulation of the potential volume of the shunt. A partial protective action of the crest might thus act to reduce the tendency to excessive pressures in the pulmonary arteries. Catheterization data in a case of Semler and Brandenburg[19] demonstrated a definite increase in systolic pressure when the catheter was withdrawn from the outflow to the inflow part of the right ventricle, indicating the presence of some degree of obstruction to outflow from the right ventricle. Further, the evidence in our case for a long-standing large shunt (loud murmur, high pulse pressure, and low diastolic pressure), and the absence of significant pulmonary vascular sclerosis suggests protection of these vessels against such high pressures.

Definitive diagnosis of these defects through clinical study and cardiac catheterization has recently become possible.[12, 13, 19] Attempts at surgical repair would appear to be indicated in some cases. A fistula between the sinus of Valsalva and the right atrium, diagnosed by aortography and cardiac catheterization, has been successfully closed by open-heart surgery.[20]

Summary

A man of 79 years with progressive congestive failure was found to have a low diastolic pressure, a wide pulse pressure, and a machinery-type murmur over the precordium. He responded repeatedly to medical therapy for congestive failure. A diagnosis of an intracardiac shunt was made about 18 months before death. Autopsy revealed a large heart with a fistula joining the sinus of Valsalva to the right ventricle immediately beneath a hypertrophied crista supraventricularis. Clinical, physiologic, and pathologic aspects of the case are discussed.

Summario in Interlingua

In un masculo de 79 annos de etate con progressive disfallimento congestive, basse tension diastolic esseva constatate insimul con un large pression de pulso e un murmure del typo de locomotiva supra le precordio. Le patiente respondeva repetitemente a therapia medical pro disfallimento congestive. Le diagnose de un shunt intracardiac esseva facite circa 18 menses ante morte. Le necropsia revelava un grande corde con un fistula inter le sino de Valsalva e le ventriculo dextere, immediatemente infra un hypertrophiate crista supraventricular. Aspectos clinic, physiologic, e pathologic del caso es discutite.

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Harvey and Sydenham, types of the scientific and the practical physician, though contemporaries, were uninfluenced, so far as we know, by each other's work or method. Harvey had little reputation as a practical physician, and Sydenham cared little for theories or experiment. Modern scientific medicine, in which these two great types meet, had its rise in France in the early days of this century. True, there had lived and worked in England the greatest anatomist and medical thinker of modern times; but John Hunter, to whose broad vision disease was but one of the processes of nature to be studied, was as a voice crying in the wilderness to the speculative, theoretical physicians of his day.—William Osler, M.D. *Influence of Louis on American Medicine.* Johns Hopkins Hospital Bulletin, 1897.

CLINICAL PROGRESS

Fever

Pathogenesis and Circulatory Changes

By W. I. Cranston, M.D., M.R.C.P.

FEVER has been recognized as a common and reliable sign of disease for many centuries, and many of the associated circulatory changes have long been known; the cold pale skin, the subsequent warmth and flushing, and the rapid pulse were well-defined clinical signs long before the introduction of the thermometer.

The first experimental approach to the nature of the stimulus responsible for fever was made at the middle of the last century, when several German workers produced fever in experimental animals by the injection of pus and blood from other infected animals. As they were unaware of the nature and dangers of bacterial contamination, it is difficult to interpret their results. One cannot but be impressed by the fact that the same general methods of study are still employed at the present time; some of this early work is described in a recent review.[1] In 1875, Von Liebermeister[2] concluded that in fever the body temperature was regulated at an abnormally high level, but that the temperature-regulating mechanism remained intact and efficient. This hypothesis has been substantiated by numerous experiments, and though it is clearly invalid in the case of the pyrexia associated with brain damage, it represents the view generally held at present. Despite some evidence to the contrary,[3] the commonly held concept of fever as a change in the setting of a central thermostat is probably as nearly correct as any other.

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Pathogenesis

During the past decade, a great deal of experimental work has been carried out in an attempt to define the stimulus that affects the temperature-regulating mechanism.

It has become apparent that pyrogenic materials can be differentiated into at least 2 groups. Bacterial pyrogens, the endotoxins of gram-negative bacteria, are typical examples of the first group. These endotoxins are obtained from gram-negative bacilli and are lipopolysaccharide in nature, though they may be associated with proteins under certain circumstances;[4] they are very stable on storage and resist autoclaving, but they can be destroyed by prolonged exposure to very high temperatures. Their ubiquity and stability are constant sources of anxiety to those involved in the preparation and use of any material for parenteral administration.

The second group, the endogenous or leukocyte pyrogens, have been obtained from extracts of normal animal leukocytes and from tissue fluids of animals that have been exposed to bacterial pyrogens or infective agents. Presently available evidence suggests that the latter type of pyrogen may be the one that affects the temperature-regulating mechanism in most, and possibly all, instances of fever associated with inflammatory conditions.

After the intravenous injection of a bacterial pyrogen into a rabbit, there is a delay of 10 to 25 minutes before the tem-

perature begins to rise; in man, the latent period is 45 to 90 minutes. Grant and Whalen[5] found that this delay was significantly shortened in rabbits, if the pyrogen (typhoid vaccine) was incubated with rabbit blood or plasma before injection. The same type of accelerated response was observed after the injection of serum obtained from febrile rabbits 3 hours after they had been injected with typhoid vaccine. It appeared that a modified, or perhaps totally different, type of pyrogen had been discovered and these authors first gave the name endogenous pyrogen to this rapidly acting material. No chemical changes have been detected in rabbit plasma after its incubation with bacterial pyrogen.[6] In man, a similar type of endogenous pyrogen can be produced if bacterial pyrogens are incubated with fresh whole blood.[7, 8] Serum and plasma are ineffective in this respect; incubation with either results in inactivation of the bacterial pyrogen,[9, 10] possibly due to the action of the properdin system. In man, the presence of white blood cells, probably granulocytes, is essential for the production of endogenous pyrogen.[11] There is evidence that endogenous pyrogens are to some extent species-specific;[12] endogenous pyrogen obtained from dogs is not pyrogenic when injected into rabbits, and vice versa.

If doses of bacterial pyrogen are injected intravenously at intervals of 1 or 2 days, the febrile response becomes progressively smaller, though it does not entirely disappear. After the injections have been discontinued, susceptibility is restored in 2 to 4 weeks. This phenomenon of tolerance is independent of specific immune mechanisms; when an animal is made tolerant to one bacterial pyrogen, it also becomes tolerant to others. It is of interest, and probably of importance, to find that such tolerant animals have an increased resistance to hemorrhage and traumatic shock.[13]

The rate of clearance of pyrogen from the peripheral blood has been measured, after the intravenous injection of typhoid vaccine.[14] Blood was drawn at intervals from the injected rabbits and the serum was then injected into previously untreated recipients; the febrile response of these recipients was used as an index of the amount of pyrogen in the donors' blood. When the vaccine was injected into donor rabbits, which had not previously been exposed to it, the amount of pyrogen in the peripheral blood fell off rapidly in the first half hour after injection, and declined with defervescence. Tolerant animals removed all of the pyrogen from their blood within a few minutes after injection. Nontolerant animals, which had been sensitized to the vaccine by its injection several weeks before, also showed a very rapid initial clearance of pyrogen from their peripheral blood, so that 30 minutes after injection no pyrogen could be detected; thereafter, pyrogenic material reappeared in the blood, and 90 minutes after injection the concentration was similar to that at 5 minutes after injection.

This pyrogen, which appeared later, had properties very different from those of the vaccine originally injected.[15] It did not give rise to tolerance if injected repeatedly; tolerant and nontolerant animals responded equally to its injection, and it was shown to be inactivated by heating to 70 C. for 30 minutes. The same type of pyrogen was also found in the peripheral blood of the first group of rabbits which had not previously received typhoid vaccine, though here its appearance was partly masked by the slower initial rate of clearance of the injected vaccine. Although this material has also been called endogenous pyrogen, there is some doubt whether it is identical with the pyrogen produced as a result of incubating bacterial pyrogen with rabbit plasma. So far as their biologic properties are concerned, there is no clear-cut differentiation between the 2, and the question of their identity must await further study.

It has been suggested that bacterial pyrogens may be cleared from the blood by the reticuloendothelial system, and that the de-

velopment of tolerance may be due to enhanced activity of this system because tolerance to typhoid vaccine was shown to be abolished by the injection of thorotrast.[16] Initial studies with radioactive endotoxin showed that tolerant rabbits cleared their plasma of radioactivity more rapidly than control animals,[17] Much of the radioactive material was found in the liver in both groups. Similar, more recent studies, with use of smaller doses of endotoxin with a higher specific activity, have shown no difference between the clearance rates in tolerant and control animals,[18] so that the role of the reticuloendothelial system in the development of tolerance is by no means clear. Another possible reason for the development of tolerance is failure or exhaustion of the process responsible for the formation of endogenous pyrogen; some evidence in support of this hypothesis has been obtained by Atkins and Huang.[19]

The whole problem of the nature of tolerance is still incompletely solved; if large doses of endotoxin are given repeatedly, tolerance does not develop, although endogenous pyrogen cannot be detected in the peripheral blood after the first or second injection. This may indicate, as has been suggested,[20] that endotoxin can have a direct effect upon the temperature-regulating center; it is difficult to establish experimentally whether this is so.

Although pyrogenic polysaccharides have been found in normal animal tissues,[21] they appear to be present in an inactive form, and their activity is only disclosed after chemical treatment; it is not known whether they are active in vivo. Their properties are similar to those of bacterial pyrogens, and it is uncertain whether they have any effect upon temperature regulation in the intact animal.

It is very doubtful whether bacterial pyrogens play an imporant direct role in the etiology of naturally occurring fever, although there is some evidence that brucella endotoxin may be responsible for the fever of brucellosis, particularly if antibacterial agents have been exhibited.[22] Menkin,[23] searching for the agent responsible for fever in animals with sterile inflammatory processes, extracted a pyrogenic euglobulin from sterile inflammatory exudate, which he called pyrexin. This substance has properties similar to those of bacterial pyrogens,[24] however, and the possibility cannot be excluded that its efficacy may be, at least in part, due to contamination with bacterial pyrogen or pyrogenic tissue polysaccharides. Bennett and Beeson,[25] carefully avoiding this pitfall, made saline extracts of many rabbit tissues and organs. Extracts of granulocytes alone proved pyrogenic on intravenous injection, and the pyrogen contained therein had properties identical with those of endogenous pyrogen, as previously described.[24] In addition, it was apparently resistant to the action of trypsin, chymotrypsin, and ribonuclease.

In all experiments involving the injection of bacterial pyrogens, it is difficult to be sure that endogenous pyrogen is the only agent responsible for fever, because of the possibility that bacterial pyrogens may have some direct action upon the temperature-regulating mechanism. Accordingly, Bennett[26] investigated fever due to pneumococcal peritonitis in rabbits, using pneumococci which themselves contained no pyrogen. By passive transfer methods, he found endogenous pyrogen in the peritoneal fluid and in the thoracic duct, but not in the peripheral blood, of febrile rabbits with pneumococcal peritonitis. If this endogenous pyrogen were responsible for the fever, it would have to be transported to the brain and thus its absence from the peripheral blood would be surprising. King and Wood[27] later employed the same preparation; by transferring larger amounts of blood, they were able to demonstrate the presence of circulating endogenous pyrogen in these animals. Atkins and Huang[28] have found endogenous pyrogen in the blood of rabbits that developed fever after the injection of viruses.

Convincing evidence has been provided to show that endogenous pyrogen, obtained either from leukocyte extracts or from the peripheral blood of animals infected with pneumococci or streptococci, acts directly upon the brain, while bacterial pyrogens do not.[29] Each preparation was injected into the ear vein and into the carotid arteries of rabbits; when bacterial pyrogens were injected, the site of injection did not affect the magnitude of the resulting fever, or the the rapidity of its onset. On the other hand, endogenous pyrogen was more effective, and exerted its effect more rapidly when injected into the carotid arteries than when injected into an ear vein. It is reasonable to assume that any diffusible material will attain a higher concentration in brain after injection into the carotid artery than after injection into the venous system. This evidence indicates that the fever response is related to the concentration of endogenous pyrogen in brain, but not to the concentration of bacterial pyrogen.

All this evidence strongly suggests that endogenous pyrogen may be formed, possibly but not certainly from granulocytes, during infection with gram-positive organisms or viruses, and that this material then affects the temperature-regulating center. There is also evidence that white cells may be concerned in the fever associated with immune hemolysis in man.[30] It is uncertain whether preformed endogenous pyrogen is merely liberated from leukocytes during injection or whether the cells produce more of this material under the stimulus of infection than they contain under normal circumstances; this question is susceptible of experimental investigation. It will be much more difficult to define the mode of action of the endogenous pyrogen upon the temperature-regulating mechanism, to decide whether it is used up during its effect or whether it acts as an enzyme; it is clearly destroyed or inactivated during defervescence, but the site of its destruction is unknown. The observation that patients with cirrhosis are usually sensitive to typhoid vaccine[31] may be suggestive in this respect.

Although there is a large body of evidence to suggest that bacterial pyrogens also cause fever by liberating endogenous pyrogen from leukocytes, there are some observations that do not entirely agree with this hypothesis. If dogs are rendered agranulocytic by treatment with nitrogen mustard, and then injected with bacterial pyrogens, they show the same temperature rise as normal dogs, although their blood contains much less endogenous pyrogen.[32] It is of course possible that there are sufficient adult or immature leukocytes in the bone marrow of such dogs to elaborate endogenous pyrogen; it is also true that the measurement of pyrogen content of blood, dependent upon rather arbitrary biological assay, is by no means accurate. Even so, it is difficult to account for the very small quantity of endogenous pyrogen found in the blood of agranulocytic dogs.

Very little is known about the chemical nature of endogenous pyrogen; its purification is rendered very difficult because of the dangers of contamination with bacterial pyrogens. So far as is known, endogenous pyrogen obtained from rabbit leukocytes contains or is associated with protein and carbohydrate moieties; it does not pass a dialysis membrane, and its effect is not modified by trypsin, chymotrypsin, or ribonuclease.[24] Human endogenous pyrogen also does not dialyze, and it probably contains protein as it is precipitable by ammonium sulfate.[33] Even though a great deal can still be found out by purely biological methods, it is obviously important to establish the nature of endogenous pyrogen as far as possible.

One other series of experiments may prove of considerable value in providing a tool for the investigation of other phenomena associated with fever. In 1957, Bennett, Petersdorf, and Keene[34] showed that bacterial pyrogen was many times more pyrogenic when injected intrathecally than when given intravenously. At the height of such a fever,

there was no pyrogenic material in the peripheral blood, and tolerance did not develop after repeated intrathecal injections. It is not altogether clear whether endogenous pyrogen is involved in this reaction. It appears likely that much of the enhanced activity of endotoxin in this situation may be due to its relatively small volume of distribution in cerebrospinal fluid and possibly brain. The failure to develop tolerance may indicate that the mechanism for clearing endotoxin from the cerebrospinal fluid system differs from that responsible for its clearance from blood. But it is of considerable interest to find that this is a situation in which a high fever develops in the absence of any circulating pyrogenic material; such a system might well be used to differentiate between direct effects due to a circulating pyrogen of any type and those due to other indirect causes.

Circulatory Changes

Pyrogen-induced fever is associated with extensive and quite characteristic changes in the circulation; almost without exception, these changes have been investigated during the fever following injection of bacterial pyrogens, and little information is available concerning the changes during fever caused by infection or by the injection of endogenous pyrogen. The lethal dose of bacterial pyrogens is generally several thousand times greater than the dose required to cause fever, and the circulatory effects of lethal doses are qualitatively very different from those of pyrogenic doses. There is as yet no evidence to show whether or not this indicates an entirely different mode of action, or merely a dosage effect, but in this discussion the 2 situations will be considered separately.

When a pyrogenic dose of endotoxin is injected intravenously into a previously unexposed animal, a period of 10 to 90 minutes elapses before any changes are detectable; the length of this delay period depends upon the type of preparation, the dose, and the species of the recipient, as previously described. The first change appears in the skin circulation. There is very marked cutaneous vasoconstriction, which, in man, precedes the elevation of central temperature by a few minutes.[7] The skin becomes pale and cold, and heat loss to the environment is greatly reduced. The same changes are apparent after the injection of endogenous pyrogen. In the rabbit, vasoconstriction is apparent in the ear. The reduction of heat loss from the skin is an important factor in the elevation of body temperature, particularly in animals; in dogs, the febrile response to the injection of bacterial pyrogens is considerably reduced by sympathectomy[35] or by adrenolytic agents,[36] but not by paralyzing doses of curare.[37] Initial experiments suggested that, in the rabbit, cutaneous vasoconstriction was unaffected or even enhanced, by sympathectomy,[38] but it was later shown clearly that these experiments had been perfo med on rabbits that were not completely sympathectomized;[39] when an adequate sympathectomy has been performed, the vasoconstriction is abolished. Ganglionic blockade with hexamethonium also prevents this vasoconstriction. In man, the cutaneous vasoconstriction is similarly abolished by sympathectomy[40] or by peripheral regional nerve block.[41] There is evidence to suggest that the increased sympathetic tone is central rather than reflex in origin.[41] When the response of the temperature-regulating mechanism is prevented by the previous administration of amidopyrine, cutaneous vasoconstriction does not occur.[42]

In man, shive ing usually begins within a period of 10 to 30 minutes after the onset of cutaneous vasoconstriction. At about this time, the cardiac output increases,[42, 43] though this increase may be preceded by a period of decreased cardiac output;[44] the heart rate accelerates; and while shivering continues, the arterial blood pressure is often slightly elevated. Thereafter, the blood pressure falls below control levels; in general, the fall of blood pressure is great, the higher the initial blood pressure level. This blood pressure fall is a manifestation of reduced peripheral resistance, as it takes place while

the cardiac output is elevated. The total peripheral resistance falls because of marked vasodilatation in the renal and splanchnic vascular beds.[42] These interesting circulatory adjustments are almost unique; the only other agent known to cause similar changes is 1-hydrazinophthalazine.[45, 46]

The renal vasodilatation was accidentally discovered by Homer Smith and his colleagues, when contaminated inulin was used in studies of renal function.[47] During the early shivering phase, there is often a short period of renal vasoconstriction, but this is rapidly followed by a marked increase in renal blood flow, which more or less runs parallel with the temperature curve, though it may persist for some time after defervescence. Renal vascular resistance may fall to less than half its control value, and there is an increase in the fraction of the cardiac output which perfuses the kidneys. A similar increase in hepatic blood flow takes place concurrently,[48] despite the fact that the function of the liver may become slightly impaired, as indicated by a decrease in the rate of clearance of injected bromsulphthalein from the blood.

The mechanism and function of these profound circulatory readjustments are poorly understood, and they require further investigation. It is apparent that the rise of body temperature is not an important factor in their inception, because they are unaffected if the rise of temperature is prevented by the previous administration of amidopyrine. Indeed, the scanty evidence available suggests that environmental heating causes a decrease in renal blood flow.[49, 50] It is known that the renal hyperemia is unaffected by sympathectomy in man[51] and in dogs;[52] so it has been suggested that a humoral mechanism is responsible. It is, of course, always difficult to assess the completeness of a surgical sympathectomy, and in this connection it would be of considerable interest to know what happens to the blood flow through a transplanted kidney during the febrile response. It has been reported that dihydroergocornine is partially effective in preventing the renal vasodilatation.[53] This finding is difficult to interpret; it is unlikely that the dihydroergocornine acts by reversing the effects of epinephrine because epinephrine alone causes renal vasoconstriction, and it is unlikely, though unproved, that its effect on the kidney is altered during the febrile reaction. The work of Thomas and his colleagues suggests that the epinephrine sensitivity of small blood vessels should be increased after the administration of pyrogenic doses of endotoxin,[54] though he has not studied these responses in renal blood vessels. If the antipyretic effect of adrenolytic agents, as previously mentioned, is merely due to a peripheral sympatholytic action, there is no obvious reason why this should affect the renal vasodilatation, which is unaffected by sympathectomy. It was suggested that dihydroergocornine might act centrally;[53] if so, its site of action is different from that of amidopyrine.

The nature of the hypothetical renal vasodilator substance is speculative; there is evidence that endotoxin may liberate serotonin,[54] and it is known that serotonin can cause some renal vasodilatation,[55] though its effect is rather variable and inconstant.[56] Its action on hepatic blood flow is unknown, but it is conceivable that it could play a part in the visceral circulatory changes associated with fever.

No information is available that throws any light upon the mechanism of the increase in hepatic blood flow, although it is known that it can be produced by very small, and almost nonpyrogenic, doses of endotoxin;[57] it is also unaffected by the administration of amidopyrine. It is unknown whether these visceral circulatory changes are dependent upon the bacterial pyrogen itself, or whether they can also be produced by the injection of endogenous pyrogen.

Cerebral blood flow is unchanged in the normal individual during pyrogen-induced fever;[58] it is maintained in the face of a fall of arterial blood pressure by a slight

decrease in cerebral vascular resistance.

It is clear that fever, even if relatively mild, may easily embarrass a circulation that is precariously balanced on the edge of cardiac failure. It would appear unlikely that treatment with antipyretics should have much effect upon cardiac failure induced in this way. There is some evidence to suggest that a persistent increase in heart size may be induced by repeated intravenous injections of bacterial pyrogens.[59] This evidence was obtained by radiologic examination of patients with neurosyphilis, who did not show any evidence of cardiovascular involvement. Electrocardiographic changes do appear during pyrogen-induced fever, but these changes are nonspecific, and probably largely due to changes in heart rate and position.[60]

Overwhelming infection and bacteremia is commonly associated with circulatory collapse, and is frequently fatal. Many attempts have been made to mimic this situation by the injection of large amounts of endotoxin, and the effects on the circulation of intravenous injection of lethal amounts of bacterial products are fairly well established. These effects are not necessarily related to the pyrogenic properties of bacterial endotoxins, because very similar circulatory changes have been observed after the injection of lethal doses of nonpyrogenic toxins or organisms.[61, 62]

The intravenous injection of lethal amounts of a bacterial pyrogen frequently causes death without elevation of body temperature: sometimes the temperature falls before death. After such an injection, in the dog, there is an immediate precipitous fall of arterial blood pressure, to very low levels.[63] Cardiac output falls correspondingly, and there is little change in the total peripheral resistance. Salivation and diarrhea may be marked, and the animal dies with circulatory failure between 2 and 24 hours after the injection. At autopsy, scattered areas of hemorrhage may be found in the skin or in any of the viscera, but the most striking changes are found in the intestine and the liver, which are deeply congested and edematous and show extensive areas of hemorrhage and necrosis.

The probable significance of these pathologic changes has been shown by Weil et al.;[3] these authors found that the portal venous pressure rose very rapidly, immediately after the intravenous injection of a lethal dose of bacterial pyrogen. There was no change, or a fall, in the hepatic vein pressure. The fall of cardiac output and systemic arterial pressure was less pronounced if the animals had previously been eviscerated, or if the liver had been excluded from the circulation. These changes were unaffected by decapitation or by transection of the spinal cord and vagi. Isolated intestinal segments, whose blood supply was intact, showed an increase in weight,[64] and it appears probable that under these circumstances a large volume of blood is trapped in the splanchnic venous bed, probably by constriction of the small intrahepatic veins and venules. There is also some evidence that blood is trapped in the lungs to a lesser extent by venoconstriction;[65] in the cat it appears that relatively less blood is sequestered in the splanchnic venous bed, and relatively more in the lungs. It has been shown that there is an increase in the vascular resistance of the isolated perfused lung when bacterial pyrogen is added to the perfusing fluid; it may be very significant that this effect can only be demonstrated when the perfusing fluid contains blood.[65] Although these circulatory changes show many similarities to those observed in anaphylactic shock, it is doubtful whether the two processes are identical; some histamine seems to be released into hepatic venous blood after the injection of pyrogen, but the amount is comparatively small.[66]

Thomas and his associates[54] have shown that bacterial endotoxins, injected intradermally or intravenously, modify the local action of epinephrine upon small blood vessels. Small doses of endotoxin cause increased sensitivity to epinephrine, but when larger doses are employed, the direct application of epinephrine to blood vessels causes vascular

dilatation and stasis, which are often followed by bleeding into the surrounding tissues. In tolerant animals, endotoxin does not alter the response to epinephrine.

The role of endotoxin is obscure; it appears to prepare or sensitize the vessels to the effects of epinephrine, although this effect differs in many respects from the Schwartzman phenomenon. Clearly this kind of effect upon the microcirculation may produce profound changes in the general circulation, but at present it is difficult to account entirely for the general circulatory changes on this basis alone.

Given a stimulus from the cerebral temperature-regulating center, possibly due to the influence of endogenous pyrogen, the peripheral circulatory changes during fever are reasonably explicable. But it is as difficult to advance any convincing reason for the visceral circulatory changes as it is to account for the elevation of body temperature itself. The general economy of biological processes might suggest that these changes are not merely useless by-products of the febrile response. It remains to be seen whether they fulfill some protective or metabolic role. But the same type of argument may be applied to fever itself; the persistence throughout homoiothermic species of a febrile response to noxious stimuli suggests that this response also is not entirely valueless. Many questions remain to be answered in this field, and many others have not yet reached the stage of formulation.

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ABSTRACTS

ATHEROSCLEROSIS

Thompson, J. S., Abraham, A., Elias, A. W., and Scott, C. C.: Observations on the Variation of Total Serum Cholesterol Levels in Normal Individuals and in Patients with Coronary Heart Disease. Am. J. M. Sc. **237**: 319 (Mar.), 1959.

Repeated total serum cholesterol measurements were made in a group of 14 patients with recent acute myocardial infarction and Dicumarol therapy and compared with the control group composed of 10 normal men. The hospital group had an average of 10 determinations made on each individual and in the control group an average of 4 determinations were made. The total serum cholesterol in the control group was 226 mg./100 ml. with a standard deviation of 29.2. In the hospital group the total serum cholesterol averaged 266 mg./100 ml. with a standard deviation of 44.6. The diet of the control group was unrestricted while the hospital group received a regular hospital diet. In both groups the determinations fell within 40 mg./100 ml. of the mean approximately 90 per cent of the time. The remaining 10 per cent of the determinations that fell outside the 40 mg./100 ml. decile may not be disregarded since 30 per cent of the control patients and 44 per cent of the hospital patients exhibited variations of this magnitude at one time or another. The per cent variation of the most deviant determination against the mean was equally variable. Individuals in the control group exhibited variations from 6-27 per cent and in the hospital group, from 3-29 per cent. Employing a t test the total serum cholesterol levels of the control group differed significantly from those of the hospital group with p equalling 0.05. On the basis of these observations the authors suggest that a minimum of 4 or 5 determinations performed on the same day should be sufficient to indicate the patient's range of variability. Once this has been established, more accurate judgment as to the efficacy of treatment may be made. Depressions of more than 20 per cent of the mean pre-treatment values (up to 400 mg./100 ml.) or of more than 50 mg./100 ml. total serum cholesterol may be taken to indicate successful depression of the serum cholesterol if the depressed levels persist.

SHEPS

Robertson, W. B.: Atherosclerosis and Ischaemic Heart-Disease. Lancet **1**: 444 (Feb. 28), 1959.

The incidence of atherosclerosis of the aorta at 500 autopsies in Jamaica was studied by a technic which allowed valid comparison with data from New Orleans and Guatemala. There was no appreciable difference between the 3 groups until after the third decade when the Jamaican and New Orleans group showed an identical upward trend not seen in the Guatemalan group until the sixth decade. In contrast to other studies, the incidence of atherosclerosis was high in Jamaica, but the incidence of ischemic heart-disease was relatively low. The Jamaican Negroes, while developing a degree of aortic atherosclerosis comparable to those in the United States only occasionally succumbed to ischemic heart-disease. Although aortic atherosclerosis was seen in its severest forms and atheroma were common in the coronaries, stenosing lesions and occlusions were uncommon. Other thrombotic diseases were similarly uncom-

mon. It is suggested that the absence of a constant relation between the incidence of atherosclerosis and the incidence of coronary thrombosis is evidence that they do not have the same cause.

KURLAND

Mitchell, J. R. A., Bronte-Stewart, B: Alimentary Lipaemia and Heparin Clearing in Ischaemic Heart-Disease. Lancet 1: 167 (Jan. 24), 1950.

The heparin activated lipemia clearing system was studied in a manner so that substrate and enzyme were kept apart until clearing could be carried out in vitro. Plasma was obtained from 12 age-matched pairs of male patients with and without ischemic heart disease at intervals after a standard fat meal. Plasma was also obtained 2 days later, after a nonfatty meal, when the clearing mechanism was activated with heparin. The plasma of patients with ischemic heart disease had higher optical densities even in fasting specimens but the difference from the normal specimens became very large at 4, 6, and 8 hours. Heparin clearing factor prepared from the ischemic heart disease patients was as active as that from the control group. There was a striking difference between the clearing of plasma lipids 2 hours and 6 hours after a fatty meal, although the initial optical densities were the same. The results suggest that the unusually intense lipemia in patients with ischemic heart disease is due to a difference in its absorption rather than to its removal.

KURLAND

Ahrens, E. G., Jr., Insull, W., Jr., Hirsch, J., Stoffel, W., Peterson, M. L., Farquhar, J. W., Miller, T., and Thomasson, H. J.: The Effect on Human Serum-Lipids of a Dietary Fat, Highly Unsaturated, but Poor in Essential Fatty Acids. Lancet 1: 115 (Jan. 17), 1959.

Although oral unsaturated fats have been repeatedly shown to reduce serum cholesterol, it has not been established whether the effects observed are related to the net unsaturation of dietary fat or to content of essential fatty acids (E.F.A.). The problem was approached by feeding a highly unsaturated marine oil (menhaden) with a low content of essential fatty acid. Two patients were studied on a metabolic ward for 21 and 22 weeks. A liquid diet was used in which the protein, fat, carbohydrate composition was 15, 40 and 45 per cent respectively of the total calories. The sole dietary fats were corn oil or menhaden oil. In both studies, serum cholesterol, phospholipids and triglycerides were reduced when corn oil was substituted for ad libitum diet. In one subject, substitution of menhaden oil for corn oil produced further reduction of serum lipids. Moreover, in both patients, the saturated acids and C19-20 polyenes which were characteristic of menhaden oil were higher in an all lipid groups during the menhaden oil diet. Since the isocalorie substitution of E.F.A.-poor menhaden oil for E.F.A.-rich corn oil produced as low or lower levels of serum-lipids, it was concluded that the presence of E.F.A. was not required to produce these serum lipid changes.

KURLAND

Kayahan, S.: Cholesterol-binding Capacity of Normal and Atherosclerotic Intimas. Lancet 1: 223 (Jan. 31), 1959.

Atherosclerotic vessels contain more than the normal quantity of lipid. This investigation was designed to determine whether this increased lipid content was due to a change in the globulins of the atherosclerotic ground-substance or to an increased entry of lipids from the blood. The intima of aorta was obtained postmortem. A saline extract was prepared for electrophoresis and chemical study. An ether extract of the intimal extract removed the lipids which could subsequently be recombined with the aqueous phase containing intimal proteins. On electrophoresis, the proteins from normal intimas separated into 3 lipid containing fractions. The atherosclerotic extracts showed only 1 fraction without electrophoretic mobility at pH 8.6. The mean cholesterol total-lipid and globulin content of atherosclerotic intima was much greater than that from normal intima. The 44 mg. cholesterol and 109 mg. total lipid combined with 1 Gm. globulin from normal intimas in contrast to 365 mg. and 1,147 mg. for globulins from atherosclerotic intimas. Thus, atherosclerotic intimas contained more lipids than normal ones. These lipids were bound to globulins which could bind more lipids than normal ones. The findings support the view that changes in the globulin of atherosclerotic intimas may account for lipid deposition in atherosclerosis.

KURLAND

Galbraith, P. A., Perry, W. F., and Beamish, R. E.: Effect of Nicotinic Acid on Serum-lipids in Normal and Atherosclerotic Subjects. Lancet 1: 222 (Jan. 31), 1959.

Large doses of nicotinic acid, 1 Gm., 3 times daily, were administered to 8 male medical students and 14 hypercholesterolemic atherosclerotic subjects. In both groups there was a signifi-

cant fall in the serum cholesterol following initiation of nicotinic acid therapy. Discontinuance was followed by a return to pretreatment values. In the 8 normal subjects β-lipoprotein lipid decreased on therapy from 73 per cent to 65 per cent of total lipoprotein lipid and in the atherosclerotic subjects from 80 per cent to 72 per cent. These changes also reverted when therapy was discontinued.

KURLAND

Mitchell, J. R. A.: Inhibition of Heparin Clearing by Patients. Lancet 1: 169 (Jan. 24), 1959.

Plasma was obtained after a fatty meal and the rate of clearing was studied after adding post-heparin plasma. Plasma obtained by fast spinning cleared more rapidly and completely than lipemic plasma produced by slow spinning. Further, by adding back the material precipitated down by fast spinning, clearing could be inhibited. A cell-free extract of platelets inhibited heparin clearing but platelet debris was minimally active. Heating and dialysis did not abolish the inhibitory properties of the extract which was also effective on the clearing of a fat emulsion.

KURLAND

Herbert, F. A., Beamish, R. E., and Perry, W. F.: Serum Cholesterol Levels in Atherosclerotic Patients Treated with Oral Anticoagulants. J. Lab. & Clin. Med. 53: 442 (Mar.), 1959.

Total serum cholesterol, total serum lipids, and beta lipoprotein were determined before and during a course of administration of the following agents to atherosclerotic patients: Group 1 consisted of 8 individuals treated with Phenylindanedione; the second group consisted of 10 patients who received Acenocoumarin; the third group consisted of 6 subjects given ethyl biscoumacetate; a fourth group consisted of 7 patients receiving no anticoagulant therapy; and a fifth group of 5 patients was treated with Heparin, 200 mg. every 48 hours subcutaneously. Determinations were done at intervals over the first 10 weeks of therapy and again over a period between 24 and 32 weeks after starting therapy. Serum cholesterol remained unchanged in the control, heparin-treated, and phenylindanedione-treated groups; while there was an initial rise in this substance followed by a return to normal in the groups treated with Acenocoumarin and ethyl biscoumacetate. The total serum lipids tended to parallel the serum cholesterol levels, although in the heparin-treated group, total serum lipids fell significantly from the pre-treatment levels but eventually returned to initial values. No significant changes were observed in the β-lipoprotein measured as a per cent of the total lipoprotein except in the subjects treated with heparin where again there was an early fall with a subsequent return to pre-treatment values.

MAXWELL

Heptinstall, R. H.: Experimental Pulmonary Atheroma. J. Path. & Bact. 77: 535 (Apr.), 1959.

Fibrin emboli were injected into rabbits after they had received a large intravenous injection of hyperlipemic serum or had been fed cholesterol for 6 days previously. It was determined that neither the 6 days of cholesterol feeding nor the emboli alone were responsible for the formation of atheroma in the pulmonary arteries. Lipid deposition occurred as a result of the acute arteritis and was found to be present as early as 24 hours after the emboli were injected. The author concluded that these experiments definitely demonstrated the importance of local vascular factors in the production of the atheromatous lesions.

KARPMAN

BLOOD COAGULATION AND THROMBOEMBOLISM

Goldowsky, S. J., and Carney, W. I.: Fatal Pulmonary Embolism. A Ten-Year Study. Am. J. Surg. 97: 274 (Mar.), 1959.

Fatal or non-fatal pulmonary embolism verified at postmortem from 1947 to 1956 were reviewed. There were 58 fatal pulmonary emboli making an incidence of 1.6 per cent of autopsies. In addition there were 206 patients with non-fatal pulmonary emboli at postmortem. The overall autopsy rate was 42.3 per cent. Among the patients with fatal embolism there were 32 women. The average age was 67.8 years (34-92), with the largest number in the 70-79 age group. There were 40 medical cases and 18 surgical cases. Nineteen of the medical patients had some form of active heart disease (e.g., failure, infarction or rheumatic disease with fibrillation) and 10 suffered from a malignant neoplasm. There were 5 cases of spontaneous primary fatal pulmonary embolism in the medical group. In the surgical group there was a relatively high incidence following hip nailing. There were 2 operations for cancer in this group. The time interval between surgery and death from embolism in the 18 surgical cases averaged 12.4 days (2-38). Two patients in the fatal group had had prophylactic vein ligations. One was a bilateral superficial

femoral vein ligation in continuity and the other had homolateral vein ligation in continuity following thigh amputation. Four patients died despite adequate anticoagulant therapy. One patient had prophyaltic bandaging of the legs. In only 1 of these latter cases was the source of the embolus verified and that was from the vena cava and left iliac vein. Among the 206 patients in whom embolism was not the prime cause of death, there were 2 patients with unilateral and 1 with bilateral superficial femoral vein ligation, all in continuity. There were 10 additional patients receiving adequate anticoagulant therapy. The source of embolism in both groups were from the heart, periprostatic veins, femoral and iliac veins, vena cava and uterine veins. In the fatal group there were only 3 patients in whom a clinical diagnosis of peripheral thrombophlebitis had been made. In addition, in only 17 cases was the diagnosis of pulmonary embolism suspected. In view of these observations, the authors suggest that once an embolus had occurred, both vein interruption and anticoagulants if feasible should be used. When phlebitis occurs in situations in which anticoagulants are unsafe or are contraindicated, exploration and interruption of the femoral vein should be carried out rather than ligation in continuity. In their experience it was not possible to determine whether a thrombus was present in an unopened vein by inspection and palpation alone. On several occasions, opening of the vein had revealed an unsuspected thrombus in a vein of normal appearance.

SHEPS

Sherry, S., Fletcher, A. P., and Alkjaersig, N.: Developments in Fibrinolytic Therapy for Thrombo-Embolic Disease. Ann. Int. Med. **50**: 560 (Mar.), 1959.

The components of the human fibrinolytic enzyme system are reviewed. The naturally occurring precursor of the fibrinolytic enzyme of the serum is called plasminogen. In the presence of an activator, this normal serum globulin is converted to plasmin. This is a proteolytic enzyme which digests fibrin into soluble polypeptides and will also digest fibrinogen, accelerator globulin and serum complement. Antiplasmins of serum and platelet inhibit the action of free plasmin in blood. The authors believe that clot lysis results from diffusion of activator into the thrombus with activation of intrinsic plasminogen. It, therefore, becomes apparent that the level of activator in the circulation, rather than the level of circulating plasmin, becomes the critical factor in controlling the rate of lysis of a thrombus. Purified streptokinase was used as the activator preparation and the level of circulating activator was controlled by an initial priming dose and a sustaining infusion. More than 50 patients with thrombo-embolic disease have been treated and evidence is available to indicate that intravascular fibrinolysis did occur in a number of instances. Emphasis is placed upon studying this form of fibrinolytic therapy in acute coronary thrombosis.

KAYDEN

Sharnoff, J. G.: Increased Pulmonary Megakaryocytes—Probable Role in Postoperative Thromboembolism. J.A.M.A. **169**: 688 (Feb. 14), 1959.

Autopsy records of 196 postoperative deaths revealed that the 60 cases ascribed to thromboembolism had significantly more megakaryocytes per unit area of lung than the 136 cases dying from other causes. It has been shown that injections of epinephrine and corticosteroids in rabbits are followed by the disappearance of megakaryocytes from the lungs. Immediately thereafter a sudden increase in circulating platelets with transient hypercoagulability of the blood is observed. Thrombocytosis may be a reflection of a stress effect in the presence of increased pulmonary megakaryocytes. It may indicate a recently existent transient blood hypercoagulability as an underlying cause of thromboembolism. This report would indicate a need for further study towards a more rational program of prevention of this frequently fatal complication.

KITCHELL

Quenneville, G., Barton, B., McDevitt, E., and Wright, I. S.: The Use of Anticoagulants for Thrombophlebitis during Pregnancy. Am. J. Obst. & Gynec. **77**: 1135 (May), 1959.

The use of anticoagulants for thrombophlebitis in 57 patients during pregnancy and in the post-partum period was reviewed. There was a high incidence of thrombo-embolic complications under conservative therapy and before effective prothrombin levels were attained. The incidence of pulmonary embolism per episode of thrombophlebitis was 6.3 per cent. Because of this, and also because extension of the local disease will produce more valvular defects in the veins and chronic venous insufficiency, prompt effective treatment of thrombophlebitis is advisable. Quick-acting anticoagulants should be used initially. Only 1 serious hemorrhagic complication occurred in a mother during anticoagulant therapy—a post-partum hemorrhage which may have been due to retained secundines. Excessive depression of coagulation in 2 instances was asso-

ciated with intrauterine death. Provided that a prothrombin concentration of 15 per cent (35 seconds in the author's laboratory) is not exceeded, coumarin derivatives can be used with relative safety. This can be achieved through the use of frequent prothrombin determinations and vitamin K_1 in small amounts by mouth whenever excessive anticoagulant effect occurs. After an episode of phlebitis, a treatment period of 6 weeks with a gradual reduction on dosage before cessation of therapy is the program of choice. Long-term anticoagulant therapy was carried out with hesitation in patients with repeated episodes of thrombophlebitis. When delivery under treatment is considered, the authors suggest that the patients be kept at a suboptimal therapeutic level of prothrombin activity near term (20-25 seconds) and their vitamin K_1 be administered at the onset of labor. In this situation vitamin K_1 should also be given to the newborn in small amounts (1-2 mg. intramuscularly per baby). In view of the high incidence of thromboembolic recurrences during the post-partum period, prophylaxis with anticoagulants seems indicated in patients who have suffered an episode of phlebitis antepartum.

SHEPS

Brafeld, A. J.: Nicoumalone: A New Anticoagulant. Brit. M. J. 1: 1211 (May 9), 1959.

Nicoumalone (Sinthrome) was used as an anticoagulant on 269 patients in this series. There were 155 cases of coronary thrombosis, 107 cases of venous thrombosis, and 7 cases of arterial occlusion. For comparison, a study was made of the records of 259 patients who received phenindione. In this series the results with nicoumalone were considered superior to those obtained with phenindione. This conclusion was based on the fact that this drug seemed to produce a higher degree of stability of the prothrombin level rather than an appraisal of the clinical results. It is suggested that this stability reduces the incidence of progressive thrombosis and spontaneous hemorrhage. The latter complication occurred in 2 patients of the series.

KRAUSE

Engler, H. S., Christopher, P. E., Williams, H. G., Spears, R. S., Moretz, W. H.: Prevention of Thrombus Formation is Small Artery Anastomoses. Arch. Surg. 78: 766 (May), 1959.

In a group of dogs in which the external diameter of the femoral arteries were 4 mm. or less, the following technics were utilized in an attempt to prevent post-operative thrombus formation: a negative electrostatic field about the anastomosis; a technice similar to that described by Linton to enlarge the area of the anastomosis; an arteriovenous fistula distal to the anastomosis is made to increase the rate of blood flow through the anastomosis; intravenous fibrinolysin, and heparinization. No benefit was demonstrated by any of these measures except heparinization. Large doses of heparin were uniformly effective in preventing thrombosis in 10 instances. Further study was planned to determine the optimum dosage and schedule to prevent thrombosis but which will not cause troublesome hemorrhage in the wound.

SHEPS

CONGENITAL ANOMALIES

Grob, M., and Kolb, E.: Congenital Aneurysm of the Coronary Artery. Arch. Dis. Child. 34: 8 (Feb.), 1959.

Case reports of 2 children with congenital aneurysms of coronary arteries are presented. The literature was extensively reviewed and a total of 36 cases were collected and summarized. The authors emphasize that the main clinical finding consists of a continuous cardiac murmur and that the pre-operative diagnosis may be made with the aid of a carefully performed angiocardiogram.

KARPMAN

CONGESTIVE HEART FAILURE

Flear, C. T. G., Hughes, P., and Quinton, A.: Red Blood Cell Electrolytes in Congestive Cardiac Failure. Acta med. scandinav. 162: 305, 1958.

The authors have determined the levels of red blood cell sodium, potassium and chloride in 33 healthy control subjects and in 69 patients with various degrees of congestive failure. The patients were on therapeutic programs which included digitalis and mercurial diuretics. Etiologic factors in the group included cor pulmonale, hypertensive, ischemic, anemic, thyrotoxic and rheumatic heart disease. A wide variation was found in the daily levels of red cell electrolytes and no significant differences were noted between the mean values for the normal subjects and for the patients in congestive failure. It was found however that a wider scatter about the mean levels existed in the patient group than in the control group although the significance of this finding was not apparent. No relationship was found between the red-cell and serum electrolyte values. No correlation existed between the red cell potassium and the total exchangeable body

potassium as determined by isotope dilution techniques. The authors conclude that the values for red blood cell electrolytes may not be used as an index of the composition of other body tissues.

FREEDBERG

Dickson, J. F., III, Hamer, N. A. J., and Dow, J. W.: Venoarterial Pumping for Relief of Intractable Cardiac Failure in Man. Arch. Surg. **87**: 418 (Mar.), 1959.

It has previously been demonstrated in animals that acute heart failure may be relieved by venoarterial pumping without an oxygenator. A case is reported in which this procedure was carried out for 26 hours in man. The patient had hemochromatosis with congestive heart failure resistant to treatment. The procedure was unsuccessful in that a diuresis was not produced. It is of interest that the apparatus was used for 26 hours with no apparent harmful effect. Except for platelet depression, no serious damage to the formed elements of the blood or coagulation mechanism was found.

SHEPS

Aviado, D. M., Jr., and Schmidt, C. F.: Physiologic Bases for the Treatment of Pulmonary Edema. J. Chron. Dis. **9**: 495 (May), 1959.

Inhalation of oxygen to minimize anoxemia is the most important and most urgent treatment of pulmonary edema, but opinion is still divided about the value of antifoaming agents as an adjunct to oxygen therapy. Treatment of the most common types of pulmonary edema uses 3 major methods of decreasing hydrostatic pressure in the pulmonary capillaries: decrease in blood flow, as with morphine, ganglion blockers, venesection, and tourniquets; increased myocardial contraction by means of digitalis or aminophylline, and dilatation of pulmonary blood vessels. Morphine, aminophylline, and isoproterenol aid also by decreasing fluctuation in intrathoracic pressure. Pulmonary edema occurring in poisoning by muscarinic drugs and anticholinesterase agents, which is steadily increasing among workers with insecticides, is treated with atropine, oxygen, and removal of fluid obstructing the air passages. Atropine is ineffective in treating an inflammatory reaction, such as caused by chlorine, bromine, or phosgene irritation. Thermal injury of the respiratory tract produces spasm in pulmonary veins and increases capillary pressure. It may become possible to treat this type of edema and also that caused by chemical injury by using improved drugs which relax vascular spasm. A new compound, 45-50, lowered pulmonary arterial pressure, raised systemic blood pressure, and slowed heart rate but has not been tested in clinical pulmonary edema. Other methods were discussed which are still in experimental stages.

MAXWELL

Olson, R. E.: Myocardial Metabolism in Congestive Heart Failure. J. Chron. Dis. **9**: 442 (May), 1959.

The biochemistry of the heart in man and experimental animals under physiologic conditions and in congestive failure is reviewed. Metabolic processes (energetics) in heart muscle are divided into 3 general phases: energy liberation, energy conservation, and energy utilization. All of these reactions must occur at adequate rates for the heart to perform work. A metabolic disturbance at any of these stages can, if it produces a generalized metabolic disease with vasodilatation, set the stage for high-output failure. Such syndromes occur as a result of oxygen lack, coenzyme lack, as seen in the thiamine-deficiency state of beriberi, or hormonal imbalance, with thyrotoxicosis being the most notable. The low-output failure seen in association with hypertension or valvular disease is related by the author to an apparent defect in actomyosin, an event of the third stage of energetics, i.e., energy utilization. The ability of the heart to do work depends on the biochemical processes which generate and utilize free energy in the process of contraction. It is therefore considered that greater precision will be possible in defining the causes of heart failure if new investigations are directed at biochemical explanations of the disease.

MAXWELL

McMichael, J.: Cardiotonics and Diuretics in Human Heart Failure. J. Chron. Dis. **9**: 602 (May), 1959.

The primary effects of digitalis are slowing of the heart, increase in strength of contractions, elevation of arterial pressure, and development of ectopic rhythms. Secondary changes are fall of venous pressure and diuresis. The types of action of the drug in various hemodynamic situations are described and illustrated. Results of efforts to strengthen contractions in the following states are discussed: mitral stenosis, mitral incompetence, hypertensive and chronic ischemic heart disease, acute ischemia, aortic stenosis and incompetence, cor pulmonale, and thyrotoxic heart failure. Theophylline is also discussed. It produced transient increases in cardiac output, being most valuable for treating acute attacks

of left ventricular failure. It helped promote a mercurial diuresis when patients had become refractory to these agents. It must always be given slowly to avoid overstimulating respiration. Diuretic therapy was discussed and the risks reviewed. Diuretics should be used with caution and at intervals of a few days to allow adjustment of electrolyte balance. Especially if edema is present, the optimum water and electrolyte balance must be carefully regulated when diuretics are used. If salt restriction or synthetic resins are part of the regimen, electrolyte imbalances are even more likely to occur. The clinician must always keep in mind the possibility of increasing uremia from sodium depletion, and muscular weakness from severe potassium loss. The author considers the safest and most physiologic approach to be treatment with digitalis alone, when this is feasible.

MAXWELL

CORONARY ARTERY DISEASE

Helander, S.: Armchair Treatment with and without Anticoagulants in Cardiac Infarction. Acta med. scandinav. **162**: 351, 1958.

In order to evaluate more fully the "armchair" method of treatment of myocardial infarction, the author studied a group of patients with myocardial infarction and divided them into 3 categories: (1) bed rest with anticoagulants, (2) armchair with anticoagulants, (3) armchair without anticoagulants. The study included 292 patients hospitalized within 3 days of the onset of the myocardial infarction and excluded those patients in whom death occurred within 24 hours of admission. The material was further divided in 3 groups on the basis of the severity of the infarction. Group I (19 per cent) included patients with shock, group II (76 per cent) included those with the usual clinical signs and symptoms of infarction while those in group III (5 per cent) could only be distinguished from angina pectoris on the basis of electrocardiographic tracings. The distribution of cases into each of the treatment groups was comparable and the total mortality figures showed 12 per cent mortality in those treated with armchair and anticoagulants, 15 per cent in armchair without anticoagulants and 26 per cent in bed rest with anticoagulants. Comparing the patients in group II the mortality rate was 6 per cent in the armchair group given anticoagulants while 16 per cent of the armchair group without anticoagulants expired. This difference was not apparent in the more severe group. In analyzing the cause of death in these patients it was found that embolism played a relatively small role as the immediate cause of death. No certain difference could be found between the incidence of thromboembolic complications in the group receiving and not receiving anticoagulant therapy. A greater number of patients died of progressive cardiac failure in the group treated with bed rest than in the group treated in a chair but the reason for this was not immediately apparent. The author suggests that the armchair treatment lessons the burden placed upon the myocardium and may decrease the risk of occurrence of pulmonary edema. It was concluded that armchair treatment was a good prophylactic measure against embolic complications so that only those patients with poor prognostic signs need be given anticoagulants.

FREEDBERG

Botham, R. J., and Young, W. P.: An Experimental Study of Systemic-Coronary Anastomosis. Surg., Gynec., & Obst. **108**: 361 (Mar.), 1959.

Two types of arterial anastomoses were carried out in a total of 25 dogs: the inferior end of an internal mammary artery into the distal end of the initial portion of the left circumflex artery and a carotid autograft between the side of the left subclavian artery and the end of the left circumflex artery. Anticoagulants were not used. Within 72 hours postoperatively, 12 animals died and had thrombosis of the graft while an additional 7 dogs succumbed, possibly of myocardial damage, but had patent grafts. Two dogs sacrificed 5½ to 6 months postoperatively had patent grafts. These results were considered to contraindicate at present an attempt to relieve segmental coronary artery disease in man by means of this type of operation.

ROGERS

Haeger, K.: Studies of the Coronary Circulation. I. The Surgical Anatomy of the Right Coronary Artery of the Dog and the Effects of Acute Ligation. J. Thoracic Surg. **37**: 517 (April), 1959.

The right coronary artery is commonly described as having 2 main branches. One branch runs along the anterior portion of the right ventricle and the margo acutus. The other runs to the posterior part of the right side of the heart. The purposes of this paper were to describe a common variant of the classical description of the distribution of the right coronary artery and to demonstrate how this variation influenced the effect on acute ligation of this vessel and some

of its branches. It was found that complete ligation of the right coronary artery resulted in death within 24 hours in 15 of 16 dogs. In 4 of 5 animals surviving the operation myocardial infarction was present at autopsy. In the mongrel dog the dominant branch was the ramus marginalis acuti and in the greyhound it was the ramus ventriculi dexter anterior. The procedure for insertion of a plastic tube in the right coronary artery required ligation of the ramus ventriculi dexter anterior. The ramus marginalis acuti was ligated in 80 dogs with no signs of difficulty. In the greyhound, where the dominant branch was the ramus ventriculi dexter anterior, ligation of this vessel resulted either in immediate ventricular fibrillation or subsequent myocardial infarction. Smaller branches of the right coronary artery could ligated without ensuing difficulty. Branches of the right coronary, therefore, can be ligated with relative impunity except for those dogs with the "greyhound" anatomy where ligation of the ramus ventriculi dexter anterior uniformly resulted in death.

LEVINSON

Wolfe, K. B.: Anatomy of the Septal Artery in Dogs' Hearts. Am. J. Surg. **97**: 279 (Mar.), 1959.

The coronary arteries in 91 dogs were injected with plastic and the tissues corroded. The septal artery arose from the left common coronary artery or at its bifurcation 50 per cent of the time. In the remaining dogs it arose from the anterior descending ramus of the left coronary artery. In these latter instances the distance between the origin of the descending ramus and the septal artery averaged 1.9 mm., and the range was from 0.5-4.5 mm. The inside diameter of the coronary arteries was also measured. The left common coronary artery averaged 4.3 mm. (2.5-8.0); the descending ramus averaged 2.7 mm. (2.0-4.0); the septal artery averaged 1.8 mm. (1.0-3.0 mm.), and the right coronary artery averaged 1.95 mm. (1.1-2.6 mm.).

SHEPS

Ensor, R. E., and Peters, H. R.: Long-Term Anticoagulant Therapy in Coronary Disease. J.A.M.A. **169**: 914 (Feb. 28), 1959.

In a series of 521 patients there was a group of 408 with myocardial infarction within which it was possible to make comparisons between 268 patients who remained on anticoagulant therapy and 140 (pseudocontrols) who discontinued such treatment after 3 months to 10 years. Mortalities at both the 5 and 10 year periods were higher for the pseudo controls (29 and 36 per cent) than for those who continued the treatment (21 and 25 per cent) The 5 year and 10 year mortality figures available in the literature in which anticoagulants were not given (true controls) are 44 and 68 per cent respectively. During the course of the study 58 minor and several rather severe hemorrhagic episodes occurred but there were no fatalities. The conclusion was reached that anticoagulant therapy improved the prognosis for the patient.

KITCHELL

Benda, L., Doneff, D., and Moses, K.: The Effect of Cocarboxylase on Rhythm Disturbances in Acute Myocardial Infarction. Cardiologia **34**: 298, 1959.

Eleven patients with acute myocardial infarction in whom arrhythmias were observed, particularly ventricular extrasystoles, are reported. In all patients the arrhythmia was rapidly relieved by intravenous administration of cocarboxylase. The source of this arrhythmia in myocardial infarction and its modification by cocarboxylase are discussed.

BRACHFELD

Maling, H. M. and Highman, B.: High Altitude Tolerance of Normal Dogs and Dogs with Myocardial Infarcts. Am. J. Physiol. **196**: 507 (Mar.), 1959.

Normal dogs, sham-operated dogs and dogs with large myocardial infarcts produced by coronary artery ligation were exposed to simulated altitudes of 34,000-38,000 feet for 3 to 3½ hours. Twelve of 13 normal dogs, and all 8 dogs with 3 to 14 day infarcts survived exposure to 34,000 feet. Five of 6 dogs with 2-day infarcts and 3 of 6 sham-operated dogs died at this exposure. There were no deaths among 8 normal dogs, and 2 deaths among 4 dogs with 7 to 18-day infarcts during exposure to 38,000 feet. Respiratory and cardiac rates increased markedly in all dogs at high altitudes. Throughout the exposures, ectopic ventricular beats were recorded frequently in most of the dogs with infarcts, less frequently in sham-operated dogs, and rarely in normal dogs. Deaths among normal and sham-operated dogs and some of the deaths among dogs with infarcts were from respiratory failure. Two deaths from ventricular fibrillation were recorded in dogs with infarcts. Exposure to high altitudes did not modify significantly either the gross or histologic appearance of the infarcts.

KAYDEN

UNCOMMON FORMS OF HEART DISEASE

Cooley, D. A., Morris, G. C., Jr., Attar, S.: Cardiac Myxoma. Arch. Surg. **87**: 410 (Mar.), 1959.

The pertinent literature is reviewed and four cases are described. In the first patient a diagnosis of constrictive pericarditis was made and when the myxoma was discovered at thoracotomy, removal was followed by cardiac arrest and death. There was presumably an embolism with tumor fragments into the pulmonary arteries. Two patients were diagnosed when operated upon for presumptive mitral stenosis. Nothing further was done in either instance at the time and subsequently, cardiopulmonary by-pass was carried out and the tumor successfully and completely removed. In the last patient a pre-operative diagnosis had been made. A successful removal was carried out utilizing cardiopulmonary by-pass.

SHEPS

Toone, E. C., Pierce, E. L., and Hennigar, G. R.: Aortitis and Aortic Regurgitation Associated with Rheumatoid Spondylitis. Am. J. Med. **26**: 255 (Feb.), 1959.

Evidence is increasing to support the opinion that a type of aortitis and aortic regurgitation is specifically related to rheumatoid spondylitis. This report describes 8 patients with aortic regurgitation and aortitis among 265 with rheumatoid spondylitis. The diagnosis of rheumatoid spondylitis was based on typical roentgenographic changes in the sacroiliac joints and characteristic physical findings. The diagnosis of aortic regurgitation was based on a diastolic murmur over the aortic valve and left sternal border. Peripheral rheumatoid arthritis was present in 5; a possible history of rheumatic fever in 1. Postmortem examination performed in 2 patients showed dilated incompetent aortic valves with shortened, thickened cusps, dilated aorta with wrinkled intima, patchy destruction of the media and endarteritis obliterans of the vasa vasorum.

KURLAND

Howard, R.: Funnel Chest: Its Effect on Cardiac Function. Arch. Dis. Child. **34**: 5 (Feb.), 1959.

The author reports on his personal experience with 400 patients afflicted with funnel chests. He concludes that exercise tolerance is improved after corrective surgery is performed and that the improvement is due to an increase in cardiac output. Angiograms of 2 patients are presented in order to demonstrate the anatomic changes produced upon the heart by the depressed sternum.

KARPMAN

OTHER SUBJECTS

Richter, K.: Pulmonary Vascular Changes in True Polycythemia. Fortschr. Röntgenstr. **90**:179 (Feb.), 1959.

Of 50 patients with polycythemia, 38 showed increased pulmonary vascular markings extending to the periphery of the lung. The degree of this increase was not strictly parallel to the severity of polycythemia. In addition to the increased vascular filling, interstitial fibrosis is partly responsible for the increased pulmonary markings. In 43 of the patients increased tortuosity of the aorta and prominence of the aortic knob and the left ventricle was found; only about 1/3 of these showed hypertension.

LEPESCHKIN

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A. CARLTON ERNSTENE, M.D.

The new President of the American Heart Association, A. Carlton Ernstene, M.D., has been active in the Association's medical programs and organizational activities for many years. He has served on the Board of Directors since 1953 and was a Vice-President in 1957-58. He has been Secretary of the Scientific Council's Executive Committee, Chairman of the Policy Committee and Chairman of the Council on Clinical Cardiology. Dr. Ernstene was a founder and first President of both the Ohio State Heart Association and the Cleveland Area Heart Society.

Born in Parker, S.D., Dr. Ernstene received his A.B. and M.D. degrees at the University of Iowa. He interned at Henry Ford Hospital, Detroit, from 1925-26 and, in 1927-28, was Resident Physician at Thorndike Memorial Laboratory, Boston City Hospital. From 1927-32, he was Instructor and Assistant in Medicine at Harvard Medical School. He served as Head of the Department of Cardiovascular Disease at Cleveland Clinic from 1932-48, when he was named to his present position as Chairman of the Clinic's Division of Medicine.

NEW OFFICERS OF ASSOCIATION ELECTED AT ANNUAL MEETING

Oglesby Paul, M.D., Clinical Associate Professor of Medicine, University of Illinois College of Medicine, was named President-elect of the American Heart Association at its recent Annual Meeting in Philadelphia. A. Carlton Ernstene, M.D., Chairman, Division of Medicine, Cleveland Clinic, was installed as the Association's President for the 1959-1960 term.

Retiring President Francis L. Chamberlain, M.D., Clinical Professor of Medicine, University of California School of Medicine, became Chairman of the Heart Association's Central Committee for Medical and Community Program.

Newly elected as Vice-Presidents of the Association were: John D. Brundage, Montclair, N.J.; J. Scott Butterworth, M.D., New York; Edgar Hull, M.D., New Orleans; Louis E. Martin, M.D., Los Angeles; Charles P. McCormick, Baltimore; and Merritt H. Stiles, M.D., Spokane. Re-elected as Vice-Presidents were: A. Wilbur Duryee, M.D., New York; Frank L. Mechem, Seattle; and Ray B. Wiser, Los Angeles.

RENEW JOURNAL SUBSCRIPTIONS THROUGH HEART ASSOCIATION

Renewals of subscriptions for 1960 of *Circulation* and *Circulation Research*, official journals published by the Association, should be made through the Publishing Director, American Heart Association, 44 East 23rd Street, New York 10, N.Y. Annual subscription rates are: *Circulation* (12 issues) $14 in the U.S. and Canada, $15 elsewhere. *Circulation Research* (6 issues) $9 in the U.S. and Canada, $10 elsewhere. (Special annual rate for full-time research fellows, $7.) Combined subscription to both journals, $21 in the U.S. and Canada, $23 elsewhere.

MEETINGS CALENDAR

February 3-6: American College of Radiology, New Orleans. William C. Stronach, 20 N. Wacker Drive, Chicago 6, Ill.

February 18-20: Central Surgical Association, Chicago. Angus D. McLachlin, Victoria Hospital, London, Ontario, Canada.

March 19-24: American Academy of General Practice, Philadelphia. Mac F. Cahal, Volker Blvd. at Brookside, Kansas City 12, Mo.

March 21-24: Southeastern Surgical Congress, New Orleans. B. T. Beasley, 1032 Hurt Bldg., Atlanta 3, Ga.

March 26-27: American Psychosomatic Society, Montreal. Eric Wittkower, 265 Nassau Road, Roosevelt, N. Y.

March 28-31: Southwestern Surgical Congress, Las Vegas. Mary O'Leary, 1213 Medical Arts Bldg., Oklahoma City, Okla.

April 1-3: American Society of Internal Medicine. San Francisco. R. L Richards, 350 Post Street, San Francisco 8, Calif.

April 3-6: American Surgical Association, White Sulphur Springs, W. Va. W. A. Altemeier, Cincinnati General Hospital, Cincinnati 29, Ohio.

April 4-9: American College of Physicians, San Francisco. E. R. Loveland, 4200 Pine Street, Philadelphia 4, Pa.

ABROAD

May 2-11: Pan American Medical Association Congress, Mexico City. Joseph J. Eller, 745 Fifth Avenue, New York 22, N. Y.

May 6-8: International Congress of Phlebology, Chambery, France. J. Marmasse, 3 Rue de la Republique, Orleans, Loiret, France.

May 15-18: International College of Surgeons, International Congress, Rome. Secretariat, 1516 Lake Shore Drive, Chicago 10, Ill.

May 23-28: Asian-Pacific Congress of Cardiology, Melbourne, Australia. A. E. Doyle, Alfred Hospital, Melbourne S. 1, Victoria, Australia.

August 14-20: Inter-American Congress of Cardiology, Rio de Janeiro. Magalhaes Gomes, Av. Nilo Pecanha, 38, Rio de Janeiro, Brazil.

August 28-September 1: International Congress on Diseases of the Chest, Vienna. A. Sattler, American College of Chest Physicians, Frankgasse 8, Vienna, Austria.

September 1-3: First International Congress of Nephrology, Geneva. G. Richet, 149 Rue de Sevres, Paris 15, France.

September 18-25: European Congress of Cardiology, Rome. Secretariat, Clinica Medica, University of Rome, Italy.

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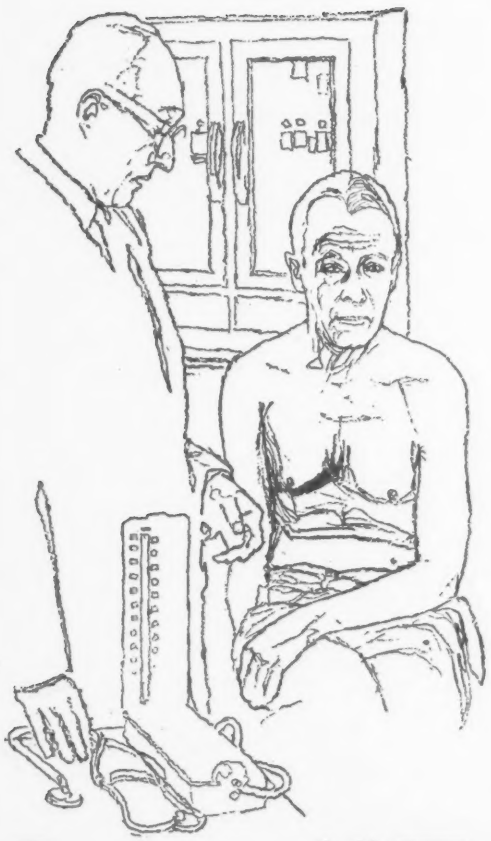

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